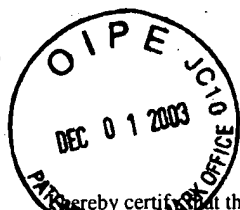


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Docket No.: PF-0232-1 DIV

Response Under 37 C.F.R. 1.116 - Expedited Procedure

Examining Group 1647

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: LaBrie et al.

Title: HUMAN TUBBY HOMOLOG

Serial No.: 09/782,390

Filing Date: February 12, 2001

Examiner: Spector, L.

Group Art Unit: 1647

Mail Stop: Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TRANSMITTAL FEE SHEET

Sir:

Transmitted herewith are the following for the above-identified application:

1. Return Receipt Postcard;
2. Brief on Appeal, including Appendix (39 pp., in triplicate);
3. Declaration of John C. Rockett, Ph.D. (10 pp., in triplicate);
4. Exhibits A - Q (in triplicate);
5. Declaration of Vishwanath R. Iyer, Ph.D. (5 pp., in triplicate); and
6. Exhibits A - E (in triplicate).

The fee has been calculated as shown below.

Claims	Claims After Amendment	Claims Previously Paid For	Present Extra	Other Than Small Entity Rate	Fee	Additional Fee(s)
Total	21	21	0	x\$18.00	\$	0
Indept.	2	3	0	x\$86.00	\$	0
First Presentation of Multiple Dependent Claims				+290.00	\$	0
Total Fee:						\$ 0

X Fee for filing a Brief in support of an Appeal under 37 CFR 1.17(c): \$ 330.00

X Please charge Deposit Account No. 09-0108 in the amount of : \$ 330.00

The Commissioner is hereby authorized to charge any additional fees required under 37 CFR 1.16 and 1.17, or credit overpayment to Deposit Account No. 09-0108. A duplicate copy of this sheet is enclosed.

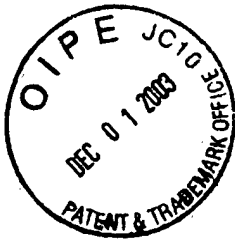
Respectfully submitted,

INCYTE CORPORATION

Date: 24 November 2003

[Signature]
Shirley A. Reardon
Reg. No. 47,016
Direct Dial Telephone: (650) 621-8555

Customer No.: 27904
3160 Porter Drive
Palo Alto, California 94304
Phone: (650) 855-0555 or Fax: (650) 845-4166

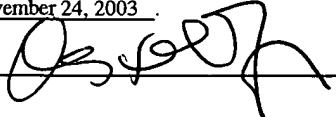


Docket No.:PF-0232-1 DIV

Response Under 37 C.F.R. 1.116 - Expedited Procedure
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By:  Printed: Katherine Stofer

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

In re Application of: LaBrie et al.

Title: HUMAN TUBBY HOMOLOG

Serial No.: 09/782,390

Filing Date: February 12, 2001

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Alexandria, Virginia 22313-1450

BRIEF ON APPEAL

Sir:

Further to the Notice of Appeal filed September 15, 2003, and received by the USPTO on September 22, 2003, herewith are three copies of Appellants' Brief on Appeal mailed on November 24, 2003, November 22, 2003 being a Saturday. Authorized fees include the \$ 330.00 fee for the filing of this Brief.

This is an appeal from the decision of the Examiner finally rejecting claims 1, 2, 16 and 17 of the above-identified application.

(1) REAL PARTY IN INTEREST

The above-identified application is assigned of record to Incyte Pharmaceuticals, Inc. (now Incyte Corporation, formerly known as Incyte Genomics, Inc.) (Reel 8689, Frame 0551), which is the real party in interest herein.

(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) STATUS OF THE CLAIMS

Claims rejected:	Claims 1, 2, 16 and 17
Claims allowed:	(none)
Claims canceled:	(none)
Claims withdrawn:	Claims 3-15 and 18-21
Claims on Appeal:	Claims 1, 2, 16 and 17 (A copy of the claims on appeal, as amended, can be found in the attached Appendix).

(4) STATUS OF AMENDMENTS AFTER FINAL

The Amendment after Final Rejection under 37 C.F.R. §1.116 filed September 15, 2003, has been entered for purposes of this appeal. See the Advisory Action mailed October 29, 2003, indicating the Amendments would be entered for purposes of Appeal.

(5) SUMMARY OF THE INVENTION

Appellants' invention is directed to a novel human tubby protein (NHT, SEQ ID NO:1) and to polypeptides comprising a naturally-occurring amino acid sequences having at least 90% identity to SEQ ID NO:1 and said polypeptide retaining at least one function of a polypeptide comprising an amino acid sequence of SEQ ID NO:1 (Specification, page 2 lines 20-23; page 11 lines 13-15). The SEQ ID NO:1 polypeptide has strong chemical and structural homology with known human tub proteins. For example:

NHT is 491 amino acids in length and as shown in Figs. 2A and 2B, has two potential N-glycosylation sites at N₁₆₂ and N₃₅₂. NHT also has potential cAMP or cGMP phosphorylation sites at R₂₄₁ and R₃₁₉. NHT has chemical and structural homology with the mouse and human tub genes (SEQ ID NO:3 and SEQ ID NO:4, respectively). In particular, NHT shares about 49% identity with the mouse and human tub proteins.

NHT and the mouse tub protein show sequence related differences in their hydrophobicity plots (Figs.3A and 3B), and the isoelectric point of NHT is 8.4, slightly more neutral than that reported for mouse. NHT was expressed in five cDNA libraries; four from brain or neuronal cell lines (CORPNOT02, HNT2RAT02, HNT2NOT01, and BRAITUT22) and one from lymph node (LNODNOT02) (Specification, page 11 lines 3 to 12; Figures 2A and 2B).

Appellants first identified sequences encoding NHT in a cDNA library prepared from an untreated HNT2 neuronal cell line. The HNT2 cell line exhibits characteristics of a committed neuronal precursor cell which is still at an early developmental stage (Specification, page 10 lines 28 to 30; page 36 line 30 to page 37 line 2).

The invention at issue is identified in the patent application as a polypeptide of SEQ ID NO:1, or variants thereof retaining at least one function of a polypeptide comprising an amino acid sequence of SEQ ID NO:1. The SEQ ID NO:1 polypeptide sequence is encoded by a gene that is expressed in humans. The novel polypeptide is demonstrated in the specification to be a member of the class of tubby proteins. In particular, SEQ ID NO:1 shares about 49% sequence identity with tubby proteins from human and mouse. Mutations in the murine *tub* gene have been associated with maturity onset diabetes, insulin resistance, progressive retinal degeneration and hearing loss. *Tub* has homology to murine phosphodiesterase and it has been suggested that sensory deficits may be associated with cGMP induced, phosphodiesterase mediated apoptotic activity (Specification page 1 line 27 to page 2 line 13).

(6) ISSUES

1. Whether claims 1, 2, 16 and 17 directed to NHT polypeptide sequences meet the utility requirement of 35 U.S.C. §101, and whether there is post-filing evidence that a 99% correlation between sequences of the claimed protein and TULP3, a protein known to have utility for functioning in signal transduction from heterotrimeric G protein coupled receptors, demonstrates a “substantial likelihood” of utility under 35 U.S.C. § 101.

2. Whether one of ordinary skill in the art would know how to use the claimed sequences, e.g., in toxicology testing, drug development, and the diagnosis of disease, so as to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph.

3. Whether the subject matter of claims 1 and 16 was described in the specification in such a way as too reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

4. Whether the subject matter of claims 1, 2, 16 and 17 particularly point out and distinctly claim the subject matter of the claimed invention, so as to satisfy the definiteness requirement of 35 U.S.C. §112, second paragraph.

5. Whether the subject matter of claims 1 and 16 are anticipated by Kleyn et al., U.S. Patent No. 5,646,040 under 35 U.S.C. §102 (e).

(7) GROUPING OF THE CLAIMS

As to Issue 1

All of the claims on appeal are grouped together.

As to Issue 2

All of the claims on appeal are grouped together.

As to Issue 3

This issue pertains to claims 1 and 16.

As to Issue 4

All of the claims on appeal are grouped together.

As to Issue 5

This issue pertains to claims 1 and 16.

(8) APPELLANTS' ARGUMENTS

ISSUE 1: The rejection of claims 1, 2, 16 and 17 under 35 U.S.C. § 101 is Improper, as the Inventions of Those Claims Have a Patentable Utility as Set Forth in the Instant Specification, and/or a Utility Well-Known to One of Ordinary Skill in the Art.

The rejection of claims 1, 2, 16 and 17 under 35 U.S.C. § 101 alleges in particular that:

- the claimed invention is not supported by either a substantial and credible asserted utility or a well-established utility.
- there appears to be no specific asserted utility for the claimed protein itself (Office Action of 9/24/02, page 3).
- there is no credible link between the disclosed NHT and any of the mentioned diseases, . . .

Even if a credible link were established for the disclosed nucleic acids, such would not be sufficient to confer utility to the protein, as it is not recognized in the art that nucleic acid levels are predictive of protein levels . . . Therefore, there is no specific, substantial and credible utility disclosed for the claimed protein and compositions, nor for antibodies that might be made using the claimed protein (Office Action of 9/24/02, page 4).

A. The rejection of claims 1, 2, 16 and 17 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well-known to one of ordinary skill in the art

The invention at issue, identified in the patent application as a novel human tubby homolog, abbreviated as NHT, is a polypeptide sequence encoded by a gene that is expressed in humans. The novel polypeptide is demonstrated in the specification to be a homolog of the murine *tub* gene family in which mutations in *tub* have been associated with maturity onset diabetes, insulin resistance, progressive retinal degeneration and hearing loss (Specification, page 2 lines 9-10; lines 20-22). As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which require knowledge of how the polypeptide actually functions.

The similarity of the claimed polypeptide to another polypeptide of known, undisputed utility by itself demonstrates utility beyond the reasonable probability required by law. NHT is, in that regard, homologous to murine tub (SEQ ID NO:3) and shares sequence similarity with the human homolog of tub (SEQ ID NO:4). In particular, NHT shares more than 49% sequence identity with both sequences over its entire length, and is nearly 70% identical with both SEQ ID NO:3 and SEQ ID NO:4, from about amino acid D187 to D436 (numbering on SEQ ID NO:1, about 249 consecutive amino acid residues) (see Specification, page 11, and Figures 2A and 2B).

This is more than enough homology to demonstrate a reasonable probability that the utility of murine tub and the human homolog of tub can be imputed to the claimed invention. It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. Brenner et al., Proc. Natl. Acad. Sci. U.S.A. 95:6073-78 (1998) (of record, see response filed December 13, 2002. Given homology in excess of 40% over many more than 70 amino acid residues, the probability that the claimed polypeptide is related to murine tub and the human homolog of tub is, accordingly, very high.

There is, in addition, direct proof of the utility of the claimed invention. Appellants have previously submitted the Declaration of Furness (see response filed December 13, 2002) describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications as they would have been understood at the time of the patent application. The Furness Declaration describes, in particular, how the claimed polypeptide can be used in protein expression analysis techniques such as 2-D PAGE gels and western blots. Using the claimed invention with these techniques, persons of ordinary skill in the art can better assess, for example, the potential toxic effect of a drug candidate. (Furness Declaration at ¶ [11]).

Additionally, Appellants further submit herewith two expert Declarations under 37 C.F.R. § 1.132, with respective attachments, the Rockett Declaration and the Iyer Declaration. The Rockett Declaration and the Iyer Declaration fully establish that, prior to the March 6, 1997 filing date of the parent application (U.S. Serial No. 08/812,824, the Labrie '824 application, now U.S. Patent No. 6,204,372, issued on March 20, 2001), it was well-established in the art that:

expression analysis is useful, *inter alia*, in drug discovery and lead optimization efforts; in toxicology, particularly toxicology studies conducted early in drug

development efforts; and in phenotypic characterization and categorization of cell types, including neoplastic cell types;

expression analysis can be performed by measuring expression of either proteins or of their encoding transcripts;

it is not necessary that the biological function of a gene be known for measurement of its expression to be useful in drug discovery and lead optimization analyses, toxicology, or molecular phenotyping experiments;

antibodies can routinely be prepared that specifically identify the protein immunogen; used as gene expression probes, such **antibodies** generate a signal that is specific to the protein, that is, produce a gene-specific expression signal; [Emphasis added]

each additional gene-specific probe used as a tool in expression analysis provides an additional gene-specific signal that could not otherwise have been detected, giving a more comprehensive, robust, higher resolution, statistically more significant, and thus more useful expression pattern in such analyses than would otherwise have been possible;

biologists, such as toxicologists, recognize the increased utility of more comprehensive, robust, higher resolution, statistically more significant results, and thus want each newly identified expressed gene to be included in such an analysis;

failure of a probe to detect changes in expression of its cognate gene (because such changes did not occur in a particular experiment) does not diminish the usefulness of the probe as a research tool, because such information is itself useful; and

failure of a probe completely to detect its cognate transcript in any particular expression analysis experiment (because the protein is not normally expressed in that sample) does not deprive the probe of usefulness to the community of users who would use it as a research tool.

The Patent Examiner does not dispute that the claimed polypeptide can be used in 2-D PAGE gels and western blots to perform drug toxicity testing. Appellants continue to assert that it is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

Consequently, as demonstrated by the Furness, Rockett and Iyer Declarations, the person of ordinary skill in the art can achieve beneficial results from the claimed polypeptide in the absence of any

knowledge as to the precise function of the protein. The uses of the claimed polypeptide for gene expression monitoring applications including toxicology testing are in fact independent of its precise function.

The Final Office Action is replete with arguments made and positions taken for the first time in a misplaced attempt to justify the rejections of the claims under 35 U.S.C. §§ 101 and 112. This is particularly so with respect to the substantial, specific and credible utilities disclosed in the Labrie '824 application relating to the use of the SEQ ID NO:1 polypeptide for protein expression monitoring applications. Such protein expression monitoring applications are highly useful in drug development and in toxicity testing.

B. The Rockett and Iyer Declarations Submitted with this Brief Must be Considered by the Examiner, as There is Good and Sufficient Reasons Under 37 CFR 1.195 Why They Were Not Earlier Submitted

The Final Office Action is replete with arguments made and positions taken for the first time in a misplaced attempt to justify the rejections of the claims under 35 U.S.C. §§ 101 and 112. This is particularly so with respect to the substantial, specific and credible utilities disclosed in the Labrie '824 application relating to the use of the SEQ ID NO:1 polypeptide for protein expression monitoring applications. Such protein expression monitoring applications are highly useful in drug development and in toxicity testing.

The Examiner's new positions and arguments include that (a) "there is no disclosure of the use of the protein [SEQ ID NO:1] in the type of drug development and toxicology testing urged by Furness. Utility must be in the form of a specific and substantial *disclosed* utility, or a well-known utility"; (b) the utility is not specific as the testing discussed by Dr. Furness can be done with any new, uncharacterized protein; (c) the utility urged by the Declarant is not substantial as there is no established correlation of expression of the protein of SEQ ID NO:1 in an eating disorder different from expression levels in a normal individual; (d) Dr. Furness, as a consultant for Incyte Pharmaceuticals, Inc. is a concerned party; (e) no new facts or evidence on the role, function or properties of the claimed protein have been presented, thus the declaration appears to be largely one of opinion"; (d) citing *In re*

Chilowsky and *In re Lindell* the Examiner concludes that any legal opinion by Furness is not entitled to any weight; and (g)

... the use of the claimed protein for 2-D PAGE in toxicology testing or drug development does not meet the requirements of 35 U.S.C. § 101 because (a) the use is not well-known, that is, not of the level of well-known use such as the use of insulin [in treatment of diabetes] (b) cannot be asserted for *any* protein, and was not asserted for the protein of SEQ ID NO:1, and (c) does not require the isolation of the protein of SEQ ID NO:1 (Final Office Action, May 15, 2003, pages 4-5).

Thus, the Examiner found the Furness Declaration insufficient to overcome the rejections under 35 U.S.C. § 101 and under 35 U.S.C. § 112, first paragraph.

Under the circumstances, Appellants are submitting with this Appeal Brief (in triplicate) a Declaration of Rockett under 37 C.F.R. § 1.132 (the Rockett Declaration) and a Declaration of Iyer under 37 C.F.R. § 1.132 (the Iyer Declaration). As we will show, the Rockett Declaration and the Iyer Declaration each show the many substantial reasons why expression monitoring in toxicity testing and drug development are well known and well established utilities for the claimed polypeptides of SEQ ID NO:1.

The fact that the Rockett Declaration and the Iyer Declaration are being submitted in response to the Office's finding of nonpersuasiveness of the Furness Declaration in the Final Office Action constitutes, by itself, "good and sufficient reasons" under 37 C.F.R. § 1.195 why these Declarations were not earlier submitted and should be admitted at this time.

I. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be

totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. See *Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross v. Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the

asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a “substantial likelihood” of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

A. Identification of Biological Function or Role of an Expressed Polypeptide is Not Required to Demonstrate Utility

The Examiner agrees with Appellants’ position that there is no requirement that “biological function” of the claimed polynucleotides be known to establish utility. However, the Office suggested that “*appellants* statements that there has been a requirement made that *appellants* disclose the biological function of the claimed nucleic acid is incorrect” (Office Action of May 15, 2003, page 3) (emphasis added) is also incorrect.

As Appellants were replying to a non-final Office Action, the Examiner’s assertion that the instant application was as of May 15, 2003, under appeal is erroneous. Therefore, the Examiner’s assertion that the instant application was under Appeal was incorrect. Appellants’ continue to respectfully request the acknowledgment and correction of this erroneous statement, in writing, for the record.

B. The Furness Declaration Supports the “Well-Established” Utilities of NHT, and thus, at Least One Utility for SEQ ID NO:1

As a preliminary mater, Appellants note that the Examiner has not stated, for the record that the Declaration of Furness has been entered into the record. Appellants respectfully request such a statement in writing, for the record to be complete regarding the Furness Declaration.

The Examiner has asserted that the Specification does not disclose the use of NHT in gene and protein expression monitoring applications, methods well-known at the time of the filing of the parent application, March 6, 1997. However, a patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 9029 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991);

Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986); MPEP § 2164.01.

In the present case, gene and protein expression monitoring applications are known by the skilled artisan to be useful in connection with drug development and monitoring the activity of drugs. Further, the skilled artisan recognizes the use of 2-D PAGE mapping in the study of protein expression and its regulation in response to drugs and toxic agents.

The Declaration of Lars Michael Furness under 37 C.F.R. § 1.132 (the Furness Declaration) was submitted in order to provide objective evidence of at least one well-established utility for the claimed invention. The Furness Declaration described some of the practical uses of the claimed polypeptides in gene and protein expression monitoring applications as they would have been understood by one of skill in the art before March 6, 1997. Further, L. Michael Furness is a recognized expert in the art, and has no interest in the outcome of this application, contrary to the allegations of the Examiner.

Thus, the Furness Declaration provides objective evidence that a person of ordinary skill in the art can achieve beneficial results from the SEQ ID NO:1 (NHT) polypeptide in the absence of any knowledge as to the precise function of the protein. The uses of the claimed polypeptides for protein expression monitoring applications including toxicology testing are in fact independent of the function of the polypeptide. Moreover, the claimed invention has numerous other uses as a research tool, each of which alone is a “substantial utility.” These include: screening libraries of pharmaceutical agents to identify those which specifically bind NHT in a variety of drug screening techniques; generating antibodies which specifically bind and can identify NHT; and titration of NHT to initially determine the effective dose in cell culture assays or in animal models. (Specification, pages 23-25, 30-31, 36 and 44). Therefore, the uses of the claimed invention in 2-D PAGE gels to assess expression of SEQ ID NO:1 in response to drugs and toxic agents and as a research tool as **disclosed** in the instant specification are well known “real-world” utilities which are credible, specific and substantial utilities attributable to the claimed invention.

C. The Rockett and Iyer Declarations Support the “Well-Established” Utilities of ALL Expressed Proteins, Including NHT, in Protein Expression Profiles Used in Toxicology Studies, Drug Development, and the Phenotypic Characterization and Categorization of Cell types, Including Neoplastic Cell Types and Thus, at Least One Utility for SEQ ID NO:1

In order to demonstrate these points, Appellants direct the Board’s attention to quotes from the Rockett and Iyer Declarations submitted herewith:

"It is widely understood among molecular and cellular biologists that protein expression levels provide complementary profiles for any given cell and cellular state."¹

"Thus, as with nucleic acid microarrays, the greater the number of proteins detectable, the greater the power of the technique; the absence or failure of a protein to change in expression levels does not diminish the usefulness of the method; and prior knowledge of the biological function of the protein is not required. As applied to protein expression profiling, these principles have been well understood since at least as early as the 1980s."²

"It is my opinion, therefore, based on the state of the art in toxicology at least since the mid-1990s -- and as regards protein profiling, even earlier -- that disclosure of the sequence of a new . . . protein, with or without knowledge of its biological function, would have been sufficient information for a toxicologist to use the . . . protein in expression profiling studies in toxicology."³

In his Declaration, Dr. Iyer explains why a person of skill in the art in 1997 would have understood that any expressed polynucleotide is useful for gene expression monitoring applications using cDNA microarrays, stating that “[t]o provide maximum versatility as a research tool, the microarray should include – and as a biologist I would want my microarray to include – each newly identified gene as a probe.” (Iyer Declaration, ¶ 9.)

The Declarations being sufficiently brief, Appellants commend them in their entirety to the Board's attention

¹ Declaration of John C. Rockett, ¶ 11.

² Declaration of John C. Rockett, ¶ 14.

³ Declaration of John C. Rockett, ¶ 18. "Use of the words 'it is my opinion' to preface what someone of ordinary skill in the art would have known does not transform the factual statements contained in the declaration into opinion testimony." *In re Alton*, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996).

II. Appellants' Evidence Demonstrates to One of Ordinary Skill in the Art that NHT is More Likely Than Not a Member of the TUBBY Protein Family

Appellants have established, and one of skill in the art would find Appellants' evidence to demonstrate that, more likely than not, NHT is a member of the TUBBY protein family. The Specification teaches that NHT shares chemical and structural sequence similarity with two TUBBY polypeptides, one from mouse (SEQ ID NO:3) and one from human (SEQ ID NO:4). In particular, NHT shares more than 49% sequence identity with both sequences over its entire length, and is nearly 70% identical with both SEQ ID NO:3 and SEQ ID NO:4, from about amino acid D187 to D436 (numbering on SEQ ID NO:1, about 249 consecutive amino acid residues) (see Specification, page 11, and Figures 2A and 2B).

The Examiner has misconstrued Appellants' and Declarant's reference to NHT as a "novel tubby homolog," citing the "art-accepted meaning of 'homologues.'" (See the Office Action of May 15, 2003, pages 5-6). Although the Examiner's definition of homolog is "art recognized," so too is Appellants' usage. The term homolog, as used in the instant application only, is a comparison of sequences of amino acids or proteins of distantly related species. Thus, the instant application refers to NHT as being a sequence *homolog* to the mouse tub gene (GI 1279766, SEQ ID NO:3) as well as sharing sequence *similarity* to the human tub homolog of the mouse tub gene (GI 1305497, SEQ ID NO:4) (see Specification, page 2, lines 20-22).

Specifically, SEQ ID NO:1 (NHT) is yet another human homolog of the murine tub gene, GI 1279766 (SEQ ID NO:3). However, SEQ ID NO:1 should not be construed to be a homolog of SEQ ID NO:4. Rather, SEQ ID NO:1 and SEQ ID NO:4 share sequence similarity. Additionally, SEQ ID NO:1 shares chemical and structural similarity with the human tub homolog (SEQ ID NO:4) of the murine tub gene (SEQ ID NO:3). Therefore, SEQ ID NO:1 shares chemical and structural homology with SEQ ID NO:3, the mouse tub gene, and is yet another homolog of the mouse tub gene.

A. The similarity of the claimed polypeptide to another of undisputed utility demonstrates utility beyond the reasonable probability required by law

Because the claimed NHT shares homology with the TUBBY gene family, a family in which the members have undisputed utility, evidence of homology can be used to show a substantial likelihood that the claimed polypeptide is similarly useful. Appellants need not show any more to demonstrate utility. Under the applicable law, once the applicant demonstrates a *prima facie* case of homology, the Examiner must accept the assertion of utility to be true unless the Examiner comes forward with evidence showing a person of ordinary skill would doubt the asserted utility could be achieved by a reasonable probability. *See In re Brana*, 51 F.3d at 1566-67; *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974).

As indicated by the final Utility Examination Guidelines (66 FR 1092, January 5, 2001), where the asserted specific, substantial and credible utility for the claimed polypeptide/protein can be based upon homology to existing proteins having an accepted utility, "the asserted utility must be accepted by the examiner unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion." Appellants submit that this Office Action failed to provide sufficient evidence or sound reasoning to rebut Appellants' asserted use of the polypeptide.

In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether the members of the class possess one utility or many. *See Brenner v. Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967); *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973).

In fact, at a recent Biotechnology Customer Partnership Meeting held at the USPTO on April 17, 2001, in a talk by Senior Examiner James Martinell, it was emphasized that Appellants' assertion that his claimed protein "is a member of a family of proteins that [is] already known based upon amino acid sequence homology" can be effective as an assertion of utility for the claimed sequence. According to Dr. Martinell, the proper question for the Examiner to ask, after searching the

prior art for the claimed protein, is "Would one of skill in the art accept that the protein has been placed in the correct family of proteins as is asserted?" The "two" [sic: three] possible answers that can be deduced from this prior art search are, according to Dr. Martinell:

- The search does not reveal any **evidence** that the family attribution made in the application is either **incorrect or may be incorrect**
 - The protein either **more likely belongs to a family other than that asserted** in the application or **likely does not belong to the family asserted** in the application
 - The search shows that the attribution is likely correct
- (From handouts of Dr. Martinell's slides distributed April 17, 2001; emphasis added)

This Office Action has failed to meet the above requirements now recognized by the USPTO. No evidence is cited particular to the claimed protein, e.g., inconsistent findings deduced from the search, upon which to base any objection to the assignment of functional homology to this family of TUBBY proteins. Indeed, there is no such evidence.

In this regard, NHT is *similar* to two TUBBY polypeptides, one from mouse (SEQ ID NO:3) and one from human (SEQ ID NO:4). In particular, NHT shares more than 49% sequence identity over 491 amino acid residues, and is in fact nearly 70% identical with the two sequences from about amino acid D187 to D436 (about 249 amino acid residues) (see specification, page 11, and Figures 2A and 2B).

This is more than enough homology to demonstrate a reasonable probability that the utility of the human TUBBY polypeptides can be imputed to the claimed invention. It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. Brenner et. al., Proc. Natl. Acad. Sci. 95:6073-78 (1998) (Reference No. 5, of record). Given homology in excess of 40% over many more than 70 amino acid residues, the probability that the claimed polypeptide is related to the human TUBBY polypeptides is, accordingly, very high. Additional studies by others of the *TUB* gene family provide further evidence that NHT is a member of the TUBBY protein family.

Appellants submitted in their response of December 13, 2002, the results of a recent BLASTP analysis of SEQ ID NO:1 verses the genpept database (NCBI, version 132). Those results were apparently disregarded by the Office. Had the Office examined the analysis, it would have been

obvious that SEQ ID NO:1 has 99% identity, from residue M1 to residue I439 to tubby-like protein 3 (TULP3, GI21618457), and from 49% to 93% sequence identity to nine additional proteins, all of which are either tubby proteins, TUB homologs, or tubby homologs from either human or mouse (Exhibit A). Clearly, one of ordinary skill in the art would find such evidence to corroborate Appellants' assertion that SEQ ID NO:1 is a member of the TUBBY protein family.

The tubby-like protein 3 has recently been shown to function in signal transduction from heterotrimeric G protein-coupled receptors (Santagata, S. *et al.* (2001) Science 292:2041-2050, Exhibit B, of record). Such a function would more likely than not be applicable to SEQ ID NO:1 as well. Clearly, this is credible, scientific evidence that one skilled in the art would more likely than not conclude that SEQ ID NO:1 is a member of the TUBBY protein family that functions in signal transduction from heterotrimeric G protein-coupled receptors, as seen by the high conservation of residues at the C-terminus.

The Office's citation of Wistow *et al.* is moot, as Appellants' have never asserted that SEQ ID NO:1 and SEQ ID NO:4 have the same biological function (Office Action of May 15, 2003, page 6). Moreover, the teachings of Wistow *et al.* have no relevance to the instant application. Wistow *et al.* address heat-shock proteins and lens crystallins, in contrast, the instant application is directed to a novel TUBBY homolog (Specification, page 2, lines 20-22). SEQ ID NO:1 is yet another homolog of the murine Tubby protein (SEQ ID NO:3) and shares sequence identity with human Tub (SEQ ID NO:4).

Thus, Appellants' have provided corroborating evidence which one of skill in the art would find more likely than not that SEQ ID NO:1 is yet another homolog to the mouse TUBBY polypeptide and a member of the TUBBY protein family. Therefore, Appellants have met the standard of proof and the Office's evidence to the contrary refuting Appellants' findings is not applicable.

It is undisputed that the claimed polypeptide is a protein having the sequence shown as SEQ ID NO:1 in the patent application and referred to as NHT in the application. Moreover, since there is a substantial likelihood that the claimed polypeptide is a member of the TUBBY gene family, and the members are indisputably useful, there is by implication a substantial likelihood that the claimed polypeptide is similarly useful. Appellants need not show any more to demonstrate utility. Therefore, the Examiner must accept Appellants' demonstration that the claimed polypeptide is a member of the

TUBBY proteins and that the utility is proven by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. *See In re Langer*, 503 F.2d 1380, 1391-1392, 183 USPQ 288 (CCPA 1974).

The final Utility Examination Guidelines further provides that

[w]hen a class of proteins is defined such that the members share a specific, substantial, and credible utility, the reasonable assignment of a new protein to the class of sufficiently conserved proteins would impute the same specific, substantial, and credible utility to the assigned protein.

This Office Action offers no evidence that the members of this class of TUBBY proteins do not share a specific, substantial functional attribute or utility, despite having structural features in common. Thus, this strongly indicates that any member of this TUBBY protein class would have some patentable utility. It follows that there is a more substantial likelihood that the claimed polypeptide also has a patentable utility, regardless of its actual function. The law has never required a patentee to prove more.

It appears from the statements of the Office Action that Appellants are being required to assert a rigorous correlation to establish the identity of NHT as a member of the TUBBY family as well as to establish a specific disease affected by NHT. However, the final Utility Examination Guidelines provides that

[A] “rigorous correlation” need not be shown in order to establish practical utility; “reasonable correlation” is sufficient. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565, 39 USPQ2d 1895, 1900 (Fed Cir. 1996).

The Examiner must accept the Appellants’ demonstration that the homology between the claimed invention and TUBBY polypeptides demonstrates utility by a reasonable probability, and additionally, that the claimed polypeptide is a member of the TUBBY gene family unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

1. SEQ ID NO:1 has the Utility of TULP3

The Office has refused to accept that 99% sequence identity between SEQ ID NO:1 and TULP3 provides a utility for SEQ ID NO:1, i.e., functioning in signal transduction from heterotrimeric G protein coupled receptors (Office Action of May 15, 2003, page 8). The Examiner offers no basis to support the Examiner's disbelief of Appellants' asserted function. Given this lack of explicit support, Appellants can only assume that the Examiner is relying on facts within her personal knowledge that lead her to disregard the proffered evidence. She is in effect holding herself out as one of ordinary skill in the art. Thus, Appellants request an affidavit from the Examiner in support of this basis for rejection, in keeping with 37 C.F.R. §104(d)(2).

2. Constructive Reduction to Practice Constitutes Conception of Utility

Appellants' constructive reduction to practice of the instant application constitutes good and sufficient conception of the utility of SEQ ID NO:1 as disclosed in the instant application. However, the Office asserts that the Santagata et al., 2001 paper is a "post-filing date, and cannot be relied upon to establish what was known about TULP proteins at the time the invention was made" (Office Action of May 15, 2003, page 9).

The instant application is replete with disclosures of functions for SEQ ID NO:1. Appellants' assertion that TUBBY proteins are involved in appetite and eating disorders is based on the function of the murine Tubby homolog (SEQ ID NO:3). So too, SEQ ID NO:1, again based on its homology to murine tubby (SEQ ID NO:3), finds additional uses by virtue of the association of Tubby with progressive retinal degeneration and hearing loss, as well as maturity onset diabetes and insulin resistance. Further, sensory defects may be associated with cGMP induced, phosphodiesterase mediated apoptotic activity (See Specification, page 2, lines 9-13). Thus, SEQ ID NO:1 also finds use in the study of ocular diseases.

B. The Office has Failed to Consider All of the Evidence Presented by Appellants to Establish Utility for the Claimed Invention

The Examiner has asserted that Appellants cannot rely upon the Santagata et al. 2001 publication, because it is a "post-filing date, and cannot be relied upon to establish what was known

about TULP proteins at the time the invention was made” (Office Action of May 15, 2003, page 9). It is Appellants’ position that the Santagata et al. paper is further **supporting evidence** that SEQ ID NO:1 is a member of the Tubby gene family. Such evidence is required to be given “due consideration.”

Section 2701.02 of Manual of Patent Examining Procedure (original 8th edition, published August, 2001, latest revision February 2003) (hereinafter “MPEP”) provides:

If a rejection under 35 U.S.C. 101 has been properly imposed, along with a corresponding rejection under 35 U.S.C. 112, first paragraph, the burden shifts to the applicant to rebut the prima facie showing. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992) (“The examiner bears the initial burden, on review of the prior art or on any other ground, of presenting a prima facie case of unpatentability. . . . After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, **by a preponderance of evidence with due consideration to persuasiveness of argument.**”). **An applicant can do this using any combination of the following: amendments to the claims, arguments or reasoning, or new evidence submitted in an affidavit or declaration under 37 CFR 1.132, or in a printed publication.** . . . (emphasis added)

If the applicant responds to the prima facie rejection, Office personnel should review the original disclosure, any evidence relied upon in establishing the prima facie showing, any claim amendments, and any new reasoning or evidence provided by the applicant in support of an asserted specific and substantial credible utility. It is essential for Office personnel to recognize, fully consider and respond to each substantive element of any response to a rejection based on lack of utility. Only where the totality of the record continues to show that the asserted utility is not specific, substantial, and credible should a rejection based on lack of utility be maintained. ***If the record as a whole would make it more likely than not that the asserted utility for the claimed invention would be considered credible by a person of ordinary skill in the art, the Office cannot maintain the rejection. In re Rinehart, 531 F.2d 1048, 1052, 189 USPQ 143, 147 (CCPA 1976).*** (emphasis added)

Id at page 2100-42-43.

Appellants’ reiterate in their entirety arguments and reasoning presented to the Office in their response filed December 13, 2002 pertaining not only to the membership of SEQ ID NO:1 in the tubby gene family, but also evidence of the function of TULP3 and therefore, more likely than not, an asserted

function and utility for SEQ ID NO:1. Appellants respectfully ask the Office to abide by the practices set forth in the MPEP and established by case law.

C. Membership in a Class of Useful Products Can Be Proof of Utility

Despite evidence that the claimed polypeptide is a member of the TUBBY gene family, whose members indisputably are useful, the Examiner refused to impute the utility of the members of the TUBBY gene family to NHT. In the Office Action of September 24, 2002, the Patent Examiner takes the position that, "[t]he assertion that the disclosed NHT has biological activities similar to known TUBBY cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities." (Office Action of September 24, 2002, page 3, ¶ 3). To demonstrate utility by membership in the class of TUBBY polypeptides, the Examiner would require that all TUBBY polypeptides possess a "common" utility.

The Examiner has not provided any evidence that any member of the TUBBY gene family, let alone a substantial number of those members, is not useful. In such circumstances the only reasonable inference is that the claimed polypeptide must be, like the other members of the TUBBY gene family, useful.

Even if the Examiner's "common utility" criterion were correct, the TUBBY gene family would meet it. It is undisputed that known members of the TUBBY gene family function in signal transduction from heterotrimeric G protein-coupled receptors. A person of ordinary skill in the art need not know any more about how the claimed invention functions in signal transduction from heterotrimeric G protein-coupled receptors to use it, and the Examiner presents no evidence to the contrary. Instead, the Examiner makes the conclusory observation that a person of ordinary skill in the art would need to know whether, for example, any given TUBBY polypeptide functions in signal transduction from heterotrimeric G protein-coupled receptors. The Examiner then goes on to assume that the only use for NHT absent knowledge as to how this member of the TUBBY gene family actually works is further study of NHT itself. However, this assumption is incorrect.

As disclosed by Appellants, knowledge that NHT is a TUBBY-like polypeptide is more than sufficient to make it useful for the diagnosis and treatment of appetite and eating disorders and ocular diseases. Indeed, NHT has been shown to be expressed in brain, neuronal and lymph node cDNA libraries. The Examiner must accept these facts to be true unless the Examiner can provide evidence or sound scientific reasoning to the contrary. But the Examiner has not done so.

D. The Patent Examiner Failed to Demonstrate That a Person of Ordinary Skill in the Art Would Reasonably Doubt the Utility of the Claimed Invention

Appellants have shown that NHT shares homology with the TUBBY gene family, a family consisting of members known to have undisputed utility, and therefore, homology can be used to show a substantial likelihood that the claimed polypeptide is similarly useful. Appellants need not show any more to demonstrate utility. Specifically, the TUBBY family includes TULP3 which shares 99% sequence identity with NHT. TULP3 has been demonstrated to function in signal transduction from heterotrimeric G protein-coupled receptors. Based on the high level of sequence homology, structural characteristics and tissue expression, Appellants have demonstrated a *prima facie* case for homology as an acceptable assertion of utility of the claimed polypeptides. Such an assertion of utility would be determined to be sound scientific reasoning by one skilled in the art. Therefore, the Examiner must accept the Appellants' demonstration by homology that the claimed polypeptide is a member of the TUBBY gene family and that the homology between the claimed invention and TUBBY polypeptides demonstrates utility by a reasonable probability, unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility.

Under the applicable law, once the applicant demonstrates a *prima facie* case of homology, the Examiner must accept the assertion of utility to be true unless the Examiner comes forward with evidence showing a person of ordinary skill would doubt the asserted utility could be achieved by a reasonable probability. *See In re Brana*, 51 F.3d at 1566; *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974).

Moreover, as indicated by the final Utility Examination Guidelines (66 FR 1092, January 5, 2001), where the asserted specific, substantial and credible utility for the claimed polypeptide/protein

can be based upon homology to existing proteins having an accepted utility, “the asserted utility must be accepted by the examiner unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion.” Appellants submit that this Office Action failed to provide sufficient evidence or sound reasoning to rebut Appellants’ asserted use of the polypeptide.

The literature cited by the Examiner *infra* is not inconsistent with the Appellants’ proof of homology by a reasonable probability. It may show that Appellants cannot prove function by homology with **certainty**, but Appellants need not meet such a rigorous standard of proof. The literature cited identifies some of the difficulties involved in predicting biological activity, or membership in a protein family, though none suggest that functional homology cannot be inferred by a reasonable probability as in this case. The Examiner rejected the pending claims on the ground that the applicant cannot “credibly” impute utility to the claimed invention based on its 49% homology to another polypeptide undisputed by the Examiner to be useful. The Examiner’s rejection is both incorrect as a matter of fact and as a matter of procedural law.

In the present case, the Office Action alleges that the amino acid sequence identity between NHT and known TUBBY proteins is insufficient to establish that NHT is a member of the TUBBY family of proteins because “[t]he assertion that the disclosed NHT has biological activities similar to known TUBBY cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities” (Office Action, filed September 24, 2002, page 3). The Examiner cites Tischer *et al.* (U.S. Patent 5,194,596), Benjamin *et al.* (1998), Vukicevic *et al.* (1996), North *et al.* (1997), Gu *et al.* (1998) and Hayes *et al.* (1998) as support to doubt Appellants’ asserted utility. Importantly, all of these documents fail to **specifically** support the outstanding rejections because none of them are specifically relevant to the TUBBY protein family. Moreover, none of them contradict Brenner’s basic rule that sequence homology in excess of 40% over 70 or more amino acid residues yields a high probability of functional homology as well. At most, these articles individually and together stand for the **general** proposition that it is difficult to make predictions about function or biological activity with certainty.

The Examiner further cited Haynes *et al.* in support of the Examiner's assertion that nucleic acid levels are not predictive of protein levels. The Northern data presented by Appellants represents evaluation of human tissue expression patterns. The Haynes *et al.* conclusion is based on the yeast *Saccharomyces cerevisiae* growing at mid-log phase, and is therefore of very limited relevance. Only 80 *S. cerevisiae* (vs. human) proteins were selected for evaluation. Nowhere is it taught that NHT was one of the proteins evaluated. Therefore, the Haynes *et al.* paper does not teach the expression levels of SEQ ID NO:1 and does not teach away from Appellants' position that SEQ ID NO:1 was expressed in brain and neuronal tissues and in lymph node tissues. Additionally, the findings of Santagata *et al.* support Appellants' assertions that expression of SEQ ID NO:1 is predominately located in the brain.

Thus, the Haynes *et al.* paper is utterly irrelevant to the instant invention. The Examiner has attempted to broadly apply a citation which does not teach Appellants' invention. This citation does not constitute either evidence or sound scientific reasoning to show that a person of ordinary skill in the art would reasonably doubt Appellants' invention lacked patentable utility.

The Office's attention is further directed to Brenner *et al.*, *supra* that teaches through exhaustive analysis of a data set of proteins with **known** structural and functional relationships and with <90% overall sequence identity, that 30% identity has been determined to be a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner *et al.*, pages 6073 and 6076.) As shown in the Figures and as discussed in the specification, SEQ ID NO:1 shares 49% identity with at least two known TUBBY proteins over at least 491 residues, and nearly 70% identity over 249 residues, vastly exceeding this threshold. Moreover, recent BLASTP analysis actually confirms that NHT is a possible splice variant of TULP-3, by demonstrating that 99% sequence identity exists between the two proteins. Since these criteria are based on a data set of known homologous proteins with shared structural and functional features, one of ordinary skill in the art would reasonably expect the polypeptides of the invention possess the evolutionarily conserved **structural and functional** characteristics of a TUBBY protein.

It is known in the art that natural selection acts to conserve protein function. Conversely, mutations that reduce or abolish protein function are usually eliminated by natural selection. Based on

these central tenets of molecular evolution, Appellants put forth that the amino acid differences among Appellants' polypeptide and the known TUBBY proteins, are likely to occur at positions of minimal functional importance, while residues that are conserved are likely those that are important for protein function. One of ordinary skill in the art would therefore conclude that, more likely than not, the level of conservation observed between Appellants' polypeptide and the two known human TUBBY proteins are indicative of a common function, and hence common utility, among these proteins.

In conclusion, the preponderance of evidence therefore does not support the Examiner's basis for the rejection of claims under 35 U.S.C. § 101. The only relevant evidence of record shows that a person of ordinary skill in the art would not doubt that the claimed polypeptide is in fact a member of the TUBBY family of proteins, which are known to have specific utility.

IV. The diagnosis and treatment of maturity onset diabetes, insulin resistance, progressive retinal degeneration and hearing loss as well as appetite and eating disorders are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. Additionally, these uses are explained, in detail, in the Furness Declaration, discussed *supra*. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

The specification teaches that NHT is a member of the TUBBY polypeptide family and that defects in *TUB* genes and in TUBBY expression have been found in maturity onset diabetes, insulin resistance, progressive retinal degeneration and hearing loss (see specification, page 2, lines 9-10). Appellants have presented evidence that the claimed invention would have the utilities of TUBBY proteins, proteins which are known to be involved in appetite and eating disorders. Therefore, one of ordinary skill in the art would conclude that, more likely than not, that NHT would also have these uses. Thus, the claimed invention meets the utility requirements under 35 U.S.C. §§ 101 and 112, first paragraph.

V. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to withdraw the rejections. To the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: “specific” utilities, which meet the statutory requirements, and “general” utilities, which do not. The Training Materials define a “specific utility” as follows:

A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as “gene probe” or “chromosome marker” would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between “specific” and “general” utilities by assessing whether the asserted utility is sufficiently “particular,” *i.e.*, unique (Training Materials at p.52) as compared to the “broad class of invention.” (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) (“With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.”).)

Such “unique” or “particular” utilities never have been required by the law. To meet the utility requirement, the invention need only be “practically useful,” *Natta*, 480 F.2d 1 at 1397, and confer a “specific benefit” on the public. *Brenner*, 383 U.S. at 534. Thus incredible “throwaway” utilities, such as trying to “patent a transgenic mouse by saying it makes great snake food,” do not meet this standard.

Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where “specific utility” is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be “definite,” not particular. *Montedison*, 664 F.2d at 375. Appellants are not aware of any court that has rejected an assertion of utility on the grounds that it is not “particular” or “unique” to the specific invention. Where courts have found utility to be too “general,” it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had “useful biological activity” was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. See *Brana, supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a “particular” type of cancer was determined to satisfy the specificity requirement). “Particularity” is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § III.B. (*Montedison*, 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of “general” utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions heretofore considered to be patentable, and that have indisputably benefitted the public, including the claimed invention. See *supra* § III.B. Thus, the Training Materials cannot be applied consistently with the law.

ISSUE 2: The Rejection of Claim 1, 2, 16 and 17 under 35 U.S.C. § 112, first paragraph is Improper to the Extent it is Based on the Improper Allegation of Lack of Patentable Utility

- A. To the extent the rejection of the claimed invention under 35 U.S.C. § 112, first paragraph, is based on the improper rejection for lack of utility under 35 U.S.C. § 101, it must be reversed.**

The rejection set forth in the Office Actions of *September 9, 2002 and May 15, 2003* is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

Appellants respectfully submit that rejections for lack of utility, based *inter alia*, on an allegation of “lack of specificity,” as set forth in the Office Actions and as justified in the Revised Interim and final Utility Guidelines and Training Materials, are not supported in the law. Neither are they scientifically correct, nor supported by any evidence or sound scientific reasoning. These rejections are alleged to be founded on facts, yet those facts are clearly distinguishable from the facts of the instant application, and indeed most if not all nucleotide and protein sequence applications. Nevertheless, the PTO is attempting to mold the facts and holdings of these prior cases, “like a nose of wax,”⁴ to target rejections of claims to polypeptide and polynucleotide sequences, as well as to claims to methods of detecting said polynucleotide sequences, where biological activity information has not been proven by laboratory experimentation, and they have done so by ignoring perfectly acceptable utilities fully disclosed in the specifications as well as well-established utilities known to those of skill in the art. As is disclosed in the specification, and even more clearly, as one of ordinary skill in the art would understand, the claimed invention has well-established, specific, substantial and credible utilities. The rejections are, therefore, improper and should be reversed.

⁴“The concept of patentable subject matter under §101 is not ‘like a nose of wax which may be turned and twisted in any direction * * *.’ *White v. Dunbar*, 119 U.S. 47, 51.” (*Parker v. Flook*, 198 USPQ 193 (US SupCt 1978))

Moreover, to the extent the above rejections were based on the Revised Interim and final Examination Guidelines and Training Materials, those portions of the Guidelines and Training Materials that form the basis for the rejections should be determined to be inconsistent with the law.

ISSUE 3: The Rejection under 35 U.S.C. §112, first paragraph Is Improper, as the Specification Provides an Adequate Written Description as Claimed

Claims 1 and 16 stand rejected under the first paragraph of 35 U.S.C. §112 for allegedly containing subject matter “not described in the specification in such a way as too reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons cited in the previous Office Action paper number 7, at pages(s) 6-7.”

The Office Action asserts that:

- . . . the specification provides SEQ ID NO: 1. No naturally occurring variants thereof are described, . . . (Office Action of September 9, 2002, page 6).
- . . . No other naturally occurring sequences have been described as obtainable from human, nor any other animal. A breadth of 90% would reasonably be expected to encompass homologues obtained from other primate species such as macaque, rhesus, gibbon, as well as from non-primate species, such as rat or mouse, giraffe, hippo or even frog or yeast, depending upon the evolutionary conservation of the protein in question (Office Action of May 15, 2003, p. 11)
- . . . There is no description of the function of the protein, such as would allow one of skill in the art to predict what portions of the disclosed sequence would be expected to be conserved. With further respect to this issue, it is a protein that is being claimed; without having a written description of all naturally occurring sequences within the metes and bounds of the claims, one would not be capable of determining whether or not a given species was claimed (Office Action of May 15, 2003, pages. 11-12)
- At page 34, appellants argue that one of ordinary skill in the art would recognize naturally occurring variants of SEQ ID NO: 1 having 90% identity to SEQ ID NO: 1; this is not true. One could certainly determine whether a protein that one had obtained from nature were 90% identical to SEQ ID NO: 1, but that same person, handed a protein in a test tube, would have no way of

determining whether that protein were 'naturally occurring' (Office Action of May 15, 2003, page 12)

This rejection is respectfully traversed.

Appellants reiterate their arguments filed December 13, 2002 and are incorporated herein as if reiterated in full.

Clearly, it appears that the Examiner has apparently confused this instant application and the responses filed by Appellants with those by another. Appellants respectfully request that the Examiner fully review the response filed December 13, 2002, especially pages 33-36 as well as the Office Action Summary (Paper #7) which indicate that the Office Action of September 24, 2002 was a non-final action and thus the comments were incorrectly addressed to "Appellant(s)". A written statement of this fact, for the record is respectfully requested.

A. The Applicable Legal Standard

The requirements necessary to fulfill the written description requirement of 35 U.S.C. § 112, first paragraph, are well established by case law.

. . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*. *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

. . . Mention of representative compounds encompassed by generic claim language *clearly is not required by Section 112 or any other provision of the statute*. But, where no explicit description of a generic invention is to be found in the specification...mention of representative compounds may provide an implicit description upon which to base generic claim language. *In re Robins*, 429 F.2d 452, 456-57, 166 USPQ 552, 555 (CCPA 1970) [emphasis added]

. . . [I]t has been consistently held that the naming of one member of such a group is not, in itself, a proper basis for a claim to the entire group. However, *it may not be necessary to enumerate a plurality of species if a genus is sufficiently*

identified in an application by ‘other appropriate language.’ In re Grimme, 274 F.2d 949, 952, 124 USPQ 499, 501 (CCPA 1960) [emphasis added]

Attention is also drawn to the Patent and Trademark Office’s own “Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1”, published January 5, 2001, which provide that:

An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., ***complete or partial structure***, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. ***If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.*** [emphasis added] [footnotes omitted]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

1. The specification provides an adequate written description of the claimed “variants” of SEQ ID NO:1

The subject matter encompassed by Claims 1 and 16 are either disclosed by the specification or conventional or well known to one skilled in the art.

Independent claim 1 recites “An isolated polypeptide selected from the group consisting of: a) a polypeptide comprising an amino acid sequence of SEQ ID NO:1, and b)a polypeptide comprising a naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, said polypeptide retaining at least one function of a polypeptide comprising an amino acid sequence of SEQ ID NO:1.” The Examiner’s position is based upon the theory that the Specification provides an adequate written description of SEQ ID NO:1 and that “One could certainly determine whether a protein that one had obtained from nature were 90% identical to SEQ ID NO: 1(Office Action of May 15, 2003). However, the Specification allegedly lacks an adequate written description

of the variant polypeptides because, “No naturally occurring variants thereof are described” (Office Action of September 24, 2002 at page 6). Appellants strongly disagree with this position.

Such a position ignores that the polypeptides recited in claim 1) *are* described in terms of their structure. That is, the claimed polypeptides are “*at least 90% identical to the amino acid sequence of SEQ ID NO:1.*” The structure of SEQ ID NO:1 is provided in the specification, for example, at pages 46-47 of the Sequence Listing and Figures 1A, 1B, 1C and 1D for SEQ ID NO:1. The phrases “percent identity” or “% identity” as well as methods for determining such identity are well known to the skilled artisan. Claim 1, as previously amended, does not encompass any peptide or protein with altered sequence, but rather is limited to those having at least 90% amino acid sequence identity to SEQ ID NO:1.

Appellants submit that this description is sufficient to describe the claimed genus based on the disclosure of the single species, SEQ ID NO:1, for reasons stated in the USPTO’s own training materials for implementation of the Written Description Guidelines under 35 USC § 112, first paragraph. In the “Synopsis of Application of Written Description Guidelines” (USPTO Website www.uspto.gov, March 1, 2000), at page 53 of these guidelines, a claim to “A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of $A \rightarrow B$ ” is considered to meet the written description requirements because:

--- procedures for making variants of SEQ ID NO:3 are conventional in the art and an assay is described which will identify all other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity are conventional in the art.

The Guidelines further state:

The single species disclosed (SEQ ID NO:3) is representative of the genus because all member have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity.

A detailed description of the chemical and structural features of SEQ ID NO:1 which contribute to the characterization of SEQ ID NO:1 and other related proteins related to the TUBBY gene family are provided, for example, at p. 11, lines 1-10 and Figures 2A, 2B, 3A and 3B. Ninety percent variants of the claimed polypeptides are described, for example, at p. 11, lines 13-15.

When provided with the detailed description as noted above, one of ordinary skill in the art “would have understood the inventor to be in possession of the claimed invention at the time of filing.” That is, one of ordinary skill in the art would recognize polypeptide sequences which are variants at least 90% identical to SEQ ID NO:1. Given a polypeptide sequence, it would be routine for one of skill in the art to recognize whether it was a variant of SEQ ID NO:1 and to determine the % identity to SEQ ID NO:1 of the variant. Accordingly, the specification provides an adequate written description of the recited variants of SEQ ID NO:1.

2. The specification provides an adequate written description as required by law

Appellants submit that case law in the area of the written description requirement of 35 U.S.C. 112, first paragraph is clear with regard to the details considered sufficient to describe a claimed genus:

. . . Mention of representative compounds encompassed by generic claim language *clearly is not required by Section 112 or any other provision of the statute*. But, where no explicit description of a generic invention is to be found in the specification . . . mention of representative compounds may provide an implicit description upon which to base generic claim language. *In re Robins*, 429 F.2d 452, 456-57, 166 USPQ 552, 555 (CCPA 1970) [emphasis added]

. . . [I]t has been consistently held that the naming of one member of such a group is not, in itself, a proper basis for a claim to the entire group. However, *it may not be necessary to enumerate a plurality of species if a genus is sufficiently identified in an application by ‘other appropriate language.’* *In re Grimme*, 274 F.2d 949, 952, 124 USPQ 499, 501 (CCPA 1960) [emphasis added]

The specification sets forth a description of the claimed polypeptide variants using “other appropriate language” as indicated above in connection with the remarks regarding an amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1”. The claimed variants have been described in terms of their relationship to the chemical structure of SEQ ID NO:1 and structural requirements at, for example, pp. 46-47 of the Sequence Listing; Figures 1A, 1B, 1C, and 1D; p. 11, lines 1-10 and Figures 2A, 2B, 3A and 3B. The specification provides a means of identifying functional variants having 90% sequence identity with SEQ ID NO:1 at, for example, p. 11, lines 1-10. Appellants therefore submit that the “genus is sufficiently identified in [the instant]

application by ‘other appropriate language’” as stated in *In re Grimme*, 274 F.2d 949, 952, 124 USPQ 499, 501 (CCPA 1960). Furthermore, Appellants submit that “a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing” as stated in the Patent and Trademark Office’s own “Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1”, published January 5, 2001. Accordingly, Claim 2 meets the statutory requirements for written description under 35 U.S.C. 112, first paragraph.

3. Conclusion

The Final Office Action failed to base its written description inquiry pertinent to the present claims in view of their scope. In particular, the subject matter of the claims of the instant application is defined in terms of the chemical structure of SEQ ID NO:1. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polypeptides defined by the present claims is adequately described, as evidenced by specific passages of the specification as set forth above. Furthermore, the Examiner has applied to the subject application a written description standard that has no basis in the law.

For at least the above reasons it is believed that Claims 1 and 16 meet the written description requirement of 35 U.S.C. § 112, first paragraph. It is therefore requested that this rejection be reversed.

ISSUE 4: The Rejection under 35 U.S.C. §112, second paragraph, for Indefiniteness is Improper, as the Specification Clearly and Distinctly Claims the Subject Matter of the “Invention” and Determines the Metes and Bounds of Claim 1

Claims 1, 2, 16 and 17 were rejected as indefinite for allegedly “failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention” and further that, “[a]s no naturally occurring sequences having 90% identity to Seq ID NO: 1 are described, the metes and bounds of claim 1 cannot be determined. It cannot be determined which 90% identical sequences are or are not naturally occurring” (Office Action of May 15, 2003, pages 12-13). The Examiner stated that “[t]he sequence and structural properties in no way reveal the origin of the molecule or its

forebears,” and [c]laims 2, 16 and 17 are rejected for depending from an indefinite claim.” (Office Action of May 15, 2003, page 13).

The standard for “definiteness” is that the claims define patentable subject matter with a reasonable degree of precision and particularity. See *In re Miller*, 169 USPQ 597, 599 (CCPA 1971); *In re Moore*, 169 USPQ 236, 238 (CCPA 1971). See also MPEP §706.03(d). In this regard, the Supreme Court has indicated that the primary purpose of claim language is to give “fair” notice of what would constitute the infringement of a claim. See *United Carbon Co. v. Binny & Smith Co.*, 317 U.S. 228, 55 USPQ 381 (1942). In other words, the basic purpose of 35 U.S.C. §112, second paragraph is to require a claim to reasonably apprise those skilled in the art of the scope of the invention defined by that claim and give fair notice of what constitutes infringement of the claim. See *Antonious v. Pro Group Inc.*, 217 USPQ 875, 877 (6th Cir. 1983).

At pages 4-5 of the specification, Appellants define “naturally occurring” as “substantially purified NHT obtained from any species, particularly mammalian, including bovine, ovine, porcine, murine, equine, and preferably human, from any source whether natural, synthetic, semi-synthetic, or recombinant” (specification, page 4 line29 to page 5 line 1). Thus, the term “naturally occurring” would be understood by one of skill in the art and even by an unskilled person of the art to be that which occurs in nature. Further, “variants” are defined at page 5, lines 9-17, as referring to “an amino acid sequence that is altered by one or more amino acids.”

Given that Appellants define “portion” as “with regard to a protein (as in “a portion of a given protein”) refers to fragments of that protein” (specification, page 8 lines 21-25), and “alteration” as, “in the polynucleotide of SEQ ID NO:2, as used herein, comprise any alteration in the sequence of polynucleotides encoding NHT including deletions, insertions, and point mutations . . .” (specification, page 9 line 30 to page 10 line 9), and the fact that Appellants separately claim variants of SEQ ID NO:1, in subsection a) and b) of claim 1, one of ordinary skill would easily understand the term “variants” to include those naturally occurring molecules which exhibit the specified degree of sequence identity over the entire length of SEQ ID NO:1.

Hence the meaning is clear, and Appellants therefore respectfully request reversal of the rejection.

ISSUE 5: The Rejection of Claims 1 and 16 under 35 U.S.C. §102 (e) is Improper, as the Cited Reference Fails to Disclose All Elements and Limitations of the Rejected Claims

Appellants traverse the rejection of claims 1 and 16 for at least the following reasons. Kleyn *et al.* do not teach either a polypeptide comprising SEQ ID NO:1 or polypeptides having 90% sequence identity to SEQ ID NO:1; therefore, claims 1 and 16 are not anticipated by Kleyn *et al.* Additionally, although not acquiescing to the stated reason for the rejections of claims 1 and 16, claim 1 c) has been deleted. The amendment removes recitation of “a biologically-active fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, said polypeptide retaining at least one function of a polypeptide comprising an amino acid sequence of SEQ ID NO:1.” Therefore, claims 1 and 16 are not anticipated by Kleyn *et al.* and reversal of this rejection is requested.

(9) CONCLUSION

Appellants respectfully submit that rejections for lack of utility based, *inter alia*, on an allegation of “lack of specificity,” as set forth in the Office Actions and as justified in the Revised Interim and final Utility Guidelines and Training Materials, are not supported in the law. Neither are they scientifically correct, nor supported by any evidence or sound scientific reasoning. These rejections are alleged to be founded on facts in court cases such as *Brenner* and *Kirk*, yet those facts are clearly distinguishable from the facts of the instant application, and indeed most if not all nucleotide and protein sequence applications. Nevertheless, the PTO is attempting to mold the facts and holdings of these prior cases, “like a nose of wax,”⁵ to target rejections of claims to polypeptide and polynucleotide sequences, as well as to claims to methods of detecting said polynucleotide sequences, where biological activity information has not been proven by laboratory experimentation, and they have done so by ignoring perfectly acceptable utilities fully disclosed in the specifications as well as well-established utilities known to those of skill in the art. As is disclosed in the specification, and even more clearly, as one of ordinary skill in the art would understand, the claimed invention has well-established, specific, substantial and credible utilities. The rejections are, therefore, improper and should be reversed.

Moreover, to the extent the above rejections were based on the Revised Interim and final Examination Guidelines and Training Materials, those portions of the Guidelines and Training Materials that form the basis for the rejections should be determined to be inconsistent with the law.

Additionally, the inexplicable lack of consideration by the Office of Appellants’ arguments and evidence presented in the response filed September 15, 2003, results in an Office Action rife with misstatements and errors as well as an incomplete examination. Thus, Appellants must waste valuable time and resources to maintain the pendency of the instant application while the Office corrects its failure to dutifully examine and establish a complete record of examination. Thus, Appellants submit that had the Office fully considered the arguments and evidence presented to the Office in the response

⁵“The concept of patentable subject matter under §101 is not ‘like a nose of wax which may be turned and twisted in any direction * * *.’ *White v. Dunbar*, 119 U.S. 47, 51.” (*Parker v. Flook*, 198 USPQ 193 (US SupCt 1978))

filed September 15, 2003, that the instantly claimed invention would have been found too met the requirements of utility, written description, definiteness and is not anticipated as evidenced by the reasons, arguments and Declarations submitted in the response filed September 15, 2003. Therefore, Appellants respectfully request that all of the outstanding grounds of rejection, as addressed in this Brief on Appeal, be reversed.

Due to the urgency of this matter and its economic and public health implications, an expedited review of this appeal is earnestly solicited.

If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108**.

This brief is enclosed in triplicate.

Respectfully submitted,

INCYTE CORPORATION

Date: 24, November 2003

Shirley A. Recipon
Shirley A. Recipon

Reg. No. 47,016

Direct Dial Telephone: (650) 621-8555

Date: 11/24/03

Cathleen M. Rocco
Cathleen M. Rocco

Reg. No. 46,172

Direct Dial Telephone: (650) 845-4587

Customer No.: 27904
3160 Porter Drive
Palo Alto, California 94304
Phone: (650) 855-0555
Fax: (650) 849-8886

Enclosures:

1. Declaration of Declaration of John C. Rockett, Ph.D., under 37 C.F.R. §1.132, with Exhibits A - Q
2. Declaration of Vishwanath R. Iyer, Ph.D., under 37 C.F.R. § 1.132 with Exhibits A - E

APPENDIX - CLAIMS ON APPEAL

Claim 1 An isolated polypeptide selected from the group consisting of:

- a) a polypeptide comprising an amino acid sequence of SEQ ID NO:1, and
- b) a polypeptide comprising a naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, said polypeptide retaining at least one function of a polypeptide comprising an amino acid sequence of SEQ ID NO:1.

Claim 2 An isolated polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:1.

Claim 16 A composition comprising a polypeptide of claim 1.

Claim 17 A composition of claim 16, wherein the polypeptide comprises the amino acid sequence of SEQ ID NO:1.

Response Under 37 C.F.R. 1.116 - Expedited Procedure
Examining Group 1647

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Mail Stop Appeal Brief-Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450 on November 24, 2003.

By:  Printed: Katherine Stofer

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

In re Application of: LaBrie et al.

Title: HUMAN TUBBY HOMOLOG

Serial No.: 09/782,390

Filing Date: February 12, 2001

Examiner: Spector, L.

Group Art Unit: 1647

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

BRIEF ON APPEAL

Sir:

Further to the Notice of Appeal filed September 15, 2003, and received by the USPTO on September 22, 2003, herewith are three copies of Appellants' Brief on Appeal mailed on November 24, 2003, November 22, 2003 being a Saturday. Authorized fees include the \$ 330.00 fee for the filing of this Brief.

This is an appeal from the decision of the Examiner finally rejecting claims 1, 2, 16 and 17 of the above-identified application.

(1) REAL PARTY IN INTEREST

The above-identified application is assigned of record to Incyte Pharmaceuticals, Inc. (now Incyte Corporation, formerly known as Incyte Genomics, Inc.) (Reel 8689, Frame 0551), which is the real party in interest herein.

(2) RELATED APPEALS AND INTERFERENCES

Appellants, their legal representative and the assignee are not aware of any related appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) STATUS OF THE CLAIMS

Claims rejected: Claims 1, 2, 16 and 17
Claims allowed: (none)
Claims canceled: (none)
Claims withdrawn: Claims 3-15 and 18-21
Claims on Appeal: Claims 1, 2, 16 and 17 (A copy of the claims on appeal, as amended, can be found in the attached Appendix).

(4) STATUS OF AMENDMENTS AFTER FINAL

The Amendment after Final Rejection under 37 C.F.R. §1.116 filed September 15, 2003, has been entered for purposes of this appeal. See the Advisory Action mailed October 29, 2003, indicating the Amendments would be entered for purposes of Appeal.

(5) SUMMARY OF THE INVENTION

Appellants' invention is directed to a novel human tubby protein (NHT, SEQ ID NO:1) and to polypeptides comprising a naturally-occurring amino acid sequences having at least 90% identity to SEQ ID NO:1 and said polypeptide retaining at least one function of a polypeptide comprising an amino acid sequence of SEQ ID NO:1 (Specification, page 2 lines 20-23; page 11 lines 13-15). The SEQ ID NO:1 polypeptide has strong chemical and structural homology with known human tub proteins. For example:

NHT is 491 amino acids in length and as shown in Figs. 2A and 2B, has two potential N-glycosylation sites at N₁₆₂ and N₃₅₂. NHT also has potential cAMP or cGMP phosphorylation sites at R₂₄₁ and R₃₁₉. NHT has chemical and structural homology with the mouse and human tub genes (SEQ ID NO:3 and SEQ ID NO:4, respectively). In particular, NHT shares about 49% identity with the mouse and human tub proteins.

NHT and the mouse tub protein show sequence related differences in their hydrophobicity plots (Figs.3A and 3B), and the isoelectric point of NHT is 8.4, slightly more neutral than that reported for mouse. NHT was expressed in five cDNA libraries; four from brain or neuronal cell lines (CORPNOT02, HNT2RAT02, HNT2NOT01, and BRAITUT22) and one from lymph node (LNODNOT02) (Specification, page 11 lines 3 to 12; Figures 2A and 2B).

Appellants first identified sequences encoding NHT in a cDNA library prepared from an untreated HNT2 neuronal cell line. The HNT2 cell line exhibits characteristics of a committed neuronal precursor cell which is still at an early developmental stage (Specification, page 10 lines 28 to 30; page 36 line 30 to page 37 line 2).

The invention at issue is identified in the patent application as a polypeptide of SEQ ID NO:1, or variants thereof retaining at least one function of a polypeptide comprising an amino acid sequence of SEQ ID NO:1. The SEQ ID NO:1 polypeptide sequence is encoded by a gene that is expressed in humans. The novel polypeptide is demonstrated in the specification to be a member of the class of tubby proteins. In particular, SEQ ID NO:1 shares about 49% sequence identity with tubby proteins from human and mouse. Mutations in the murine *tub* gene have been associated with maturity onset diabetes, insulin resistance, progressive retinal degeneration and hearing loss. *Tub* has homology to murine phosphodiesterase and it has been suggested that sensory deficits may be associated with cGMP induced, phosphodiesterase mediated apoptotic activity (Specification page 1 line 27 to page 2 line 13).

(6) ISSUES

1. Whether claims 1, 2, 16 and 17 directed to NHT polypeptide sequences meet the utility requirement of 35 U.S.C. §101, and whether there is post-filing evidence that a 99% correlation between sequences of the claimed protein and TULP3, a protein known to have utility for functioning in signal transduction from heterotrimeric G protein coupled receptors, demonstrates a "substantial likelihood" of utility under 35 U.S.C. § 101.

2. Whether one of ordinary skill in the art would know how to use the claimed sequences, e.g., in toxicology testing, drug development, and the diagnosis of disease, so as to satisfy the enablement requirement of 35 U.S.C. §112, first paragraph.

3. Whether the subject matter of claims 1 and 16 was described in the specification in such a way as too reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

4. Whether the subject matter of claims 1, 2, 16 and 17 particularly point out and distinctly claim the subject matter of the claimed invention, so as to satisfy the definiteness requirement of 35 U.S.C. §112, second paragraph.

5. Whether the subject matter of claims 1 and 16 are anticipated by Kleyn et al., U.S. Patent No. 5,646,040 under 35 U.S.C. §102 (e).

(7) GROUPING OF THE CLAIMS

As to Issue 1

All of the claims on appeal are grouped together.

As to Issue 2

All of the claims on appeal are grouped together.

As to Issue 3

This issue pertains to claims 1 and 16.

As to Issue 4

All of the claims on appeal are grouped together.

As to Issue 5

This issue pertains to claims 1 and 16.

(8) APPELLANTS' ARGUMENTS

ISSUE 1: The rejection of claims 1, 2, 16 and 17 under 35 U.S.C. § 101 is Improper, as the Inventions of Those Claims Have a Patentable Utility as Set Forth in the Instant Specification, and/or a Utility Well-Known to One of Ordinary Skill in the Art.

The rejection of claims 1, 2, 16 and 17 under 35 U.S.C. § 101 alleges in particular that:

- the claimed invention is not supported by either a substantial and credible asserted utility or a well-established utility.
- there appears to be no specific asserted utility for the claimed protein itself (Office Action of 9/24/02, page 3).
- there is no credible link between the disclosed NHT and any of the mentioned diseases, . . .

Even if a credible link were established for the disclosed nucleic acids, such would not be sufficient to confer utility to the protein, as it is not recognized in the art that nucleic acid levels are predictive of protein levels . . . Therefore, there is no specific, substantial and credible utility disclosed for the claimed protein and compositions, nor for antibodies that might be made using the claimed protein (Office Action of 9/24/02, page 4).

A. The rejection of claims 1, 2, 16 and 17 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well-known to one of ordinary skill in the art

The invention at issue, identified in the patent application as a novel human tubby homolog, abbreviated as NHT, is a polypeptide sequence encoded by a gene that is expressed in humans. The novel polypeptide is demonstrated in the specification to be a homolog of the murine *tub* gene family in which mutations in *tub* have been associated with maturity onset diabetes, insulin resistance, progressive retinal degeneration and hearing loss (Specification, page 2 lines 9-10; lines 20-22). As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which require knowledge of how the polypeptide actually functions.

The similarity of the claimed polypeptide to another polypeptide of known, undisputed utility by itself demonstrates utility beyond the reasonable probability required by law. NHT is, in that regard, homologous to murine tub (SEQ ID NO:3) and shares sequence similarity with the human homolog of tub (SEQ ID NO:4). In particular, NHT shares more than 49% sequence identity with both sequences over its entire length, and is nearly 70% identical with both SEQ ID NO:3 and SEQ ID NO:4, from about amino acid D187 to D436 (numbering on SEQ ID NO:1, about 249 consecutive amino acid residues) (see Specification, page 11, and Figures 2A and 2B).

This is more than enough homology to demonstrate a reasonable probability that the utility of murine tub and the human homolog of tub can be imputed to the claimed invention. It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. Brenner et al., Proc. Natl. Acad. Sci. U.S.A. 95:6073-78 (1998) (of record, see response filed December 13, 2002. Given homology in excess of 40% over many more than 70 amino acid residues, the probability that the claimed polypeptide is related to murine tub and the human homolog of tub is, accordingly, very high.

There is, in addition, direct proof of the utility of the claimed invention. Appellants have previously submitted the Declaration of Furness (see response filed December 13, 2002) describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications as they would have been understood at the time of the patent application. The Furness Declaration describes, in particular, how the claimed polypeptide can be used in protein expression analysis techniques such as 2-D PAGE gels and western blots. Using the claimed invention with these techniques, persons of ordinary skill in the art can better assess, for example, the potential toxic effect of a drug candidate. (Furness Declaration at ¶ [11]).

Additionally, Appellants further submit herewith two expert Declarations under 37 C.F.R. § 1.132, with respective attachments, the Rockett Declaration and the Iyer Declaration. The Rockett Declaration and the Iyer Declaration fully establish that, prior to the March 6, 1997 filing date of the parent application (U.S. Serial No. 08/812,824, the Labrie '824 application, now U.S. Patent No. 6,204,372, issued on March 20, 2001), it was well-established in the art that:

expression analysis is useful, *inter alia*, in drug discovery and lead optimization efforts; in toxicology, particularly toxicology studies conducted early in drug

development efforts; and in phenotypic characterization and categorization of cell types, including neoplastic cell types;

expression analysis can be performed by measuring expression of either proteins or of their encoding transcripts;

it is not necessary that the biological function of a gene be known for measurement of its expression to be useful in drug discovery and lead optimization analyses, toxicology, or molecular phenotyping experiments;

antibodies can routinely be prepared that specifically identify the protein immunogen; used as gene expression probes, such **antibodies** generate a signal that is specific to the protein, that is, produce a gene-specific expression signal; [Emphasis added]

each additional gene-specific probe used as a tool in expression analysis provides an additional gene-specific signal that could not otherwise have been detected, giving a more comprehensive, robust, higher resolution, statistically more significant, and thus more useful expression pattern in such analyses than would otherwise have been possible;

biologists, such as toxicologists, recognize the increased utility of more comprehensive, robust, higher resolution, statistically more significant results, and thus want each newly identified expressed gene to be included in such an analysis;

failure of a probe to detect changes in expression of its cognate gene (because such changes did not occur in a particular experiment) does not diminish the usefulness of the probe as a research tool, because such information is itself useful; and

failure of a probe completely to detect its cognate transcript in any particular expression analysis experiment (because the protein is not normally expressed in that sample) does not deprive the probe of usefulness to the community of users who would use it as a research tool.

The Patent Examiner does not dispute that the claimed polypeptide can be used in 2-D PAGE gels and western blots to perform drug toxicity testing. Appellants continue to assert that it is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

Consequently, as demonstrated by the Furness, Rockett and Iyer Declarations, the person of ordinary skill in the art can achieve beneficial results from the claimed polypeptide in the absence of any

knowledge as to the precise function of the protein. The uses of the claimed polypeptide for gene expression monitoring applications including toxicology testing are in fact independent of its precise function.

The Final Office Action is replete with arguments made and positions taken for the first time in a misplaced attempt to justify the rejections of the claims under 35 U.S.C. §§ 101 and 112. This is particularly so with respect to the substantial, specific and credible utilities disclosed in the Labrie '824 application relating to the use of the SEQ ID NO:1 polypeptide for protein expression monitoring applications. Such protein expression monitoring applications are highly useful in drug development and in toxicity testing.

B. The Rockett and Iyer Declarations Submitted with this Brief Must be Considered by the Examiner, as There is Good and Sufficient Reasons Under 37 CFR 1.195 Why They Were Not Earlier Submitted

The Final Office Action is replete with arguments made and positions taken for the first time in a misplaced attempt to justify the rejections of the claims under 35 U.S.C. §§ 101 and 112. This is particularly so with respect to the substantial, specific and credible utilities disclosed in the Labrie '824 application relating to the use of the SEQ ID NO:1 polypeptide for protein expression monitoring applications. Such protein expression monitoring applications are highly useful in drug development and in toxicity testing.

The Examiner's new positions and arguments include that (a) "there is no disclosure of the use of the protein [SEQ ID NO:1] in the type of drug development and toxicology testing urged by Furness. Utility must be in the form of a specific and substantial *disclosed* utility, or a well-known utility"; (b) the utility is not specific as the testing discussed by Dr. Furness can be done with any new, uncharacterized protein; (c) the utility urged by the Declarant is not substantial as there is no established correlation of expression of the protein of SEQ ID NO:1 in an eating disorder different from expression levels in a normal individual; (d) Dr. Furness, as a consultant for Incyte Pharmaceuticals, Inc. is a concerned party; (e) no new facts or evidence on the role, function or properties of the claimed protein have been presented, thus the declaration appears to be largely one of opinion"; (d) citing *In re*

Chilowsky and *In re Lindell* the Examiner concludes that any legal opinion by Furness is not entitled to any weight; and (g)

... the use of the claimed protein for 2-D PAGE in toxicology testing or drug development does not meet the requirements of 35 U.S.C. § 101 because (a) the use is not well-known, that is, not of the level of well-known use such as the use of insulin [in treatment of diabetes] (b) cannot be asserted for *any* protein, and was not asserted for the protein of SEQ ID NO:1, and (c) does not require the isolation of the protein of SEQ ID NO:1 (Final Office Action, May 15, 2003, pages 4-5).

Thus, the Examiner found the Furness Declaration insufficient to overcome the rejections under 35 U.S.C. § 101 and under 35 U.S.C. § 112, first paragraph.

Under the circumstances, Appellants are submitting with this Appeal Brief (in triplicate) a Declaration of Rockett under 37 C.F.R. § 1.132 (the Rockett Declaration) and a Declaration of Iyer under 37 C.F.R. § 1.132 (the Iyer Declaration). As we will show, the Rockett Declaration and the Iyer Declaration each show the many substantial reasons why expression monitoring in toxicity testing and drug development are well known and well established utilities for the claimed polypeptides of SEQ ID NO:1.

The fact that the Rockett Declaration and the Iyer Declaration are being submitted in response to the Office's finding of nonpersuasiveness of the Furness Declaration in the Final Office Action constitutes, by itself, "good and sufficient reasons" under 37 C.F.R. § 1.195 why these Declarations were not earlier submitted and should be admitted at this time.

I. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be

totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. See *Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross v. Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examination Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the

asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a “substantial likelihood” of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

A. Identification of Biological Function or Role of an Expressed Polypeptide is Not Required to Demonstrate Utility

The Examiner agrees with Appellants’ position that there is no requirement that “biological function” of the claimed polynucleotides be known to establish utility. However, the Office suggested that “*appellants* statements that there has been a requirement made that *appellants* disclose the biological function of the claimed nucleic acid is incorrect” (Office Action of May 15, 2003, page 3) (emphasis added) is also incorrect.

As Appellants were replying to a non-final Office Action, the Examiner’s assertion that the instant application was as of May 15, 2003, under appeal is erroneous. Therefore, the Examiner’s assertion that the instant application was under Appeal was incorrect. Appellants’ continue to respectfully request the acknowledgment and correction of this erroneous statement, in writing, for the record.

B. The Furness Declaration Supports the “Well-Established” Utilities of NHT, and thus, at Least One Utility for SEQ ID NO:1

As a preliminary matter, Appellants note that the Examiner has not stated, for the record that the Declaration of Furness has been entered into the record. Appellants respectfully request such a statement in writing, for the record to be complete regarding the Furness Declaration.

The Examiner has asserted that the Specification does not disclose the use of NHT in gene and protein expression monitoring applications, methods well-known at the time of the filing of the parent application, March 6, 1997. However, a patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 9029 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991);

Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986); MPEP § 2164.01.

In the present case, gene and protein expression monitoring applications are known by the skilled artisan to be useful in connection with drug development and monitoring the activity of drugs. Further, the skilled artisan recognizes the use of 2-D PAGE mapping in the study of protein expression and its regulation in response to drugs and toxic agents.

The Declaration of Lars Michael Furness under 37 C.F.R. § 1.132 (the Furness Declaration) was submitted in order to provide objective evidence of at least one well-established utility for the claimed invention. The Furness Declaration described some of the practical uses of the claimed polypeptides in gene and protein expression monitoring applications as they would have been understood by one of skill in the art before March 6, 1997. Further, L. Michael Furness is a recognized expert in the art, and has no interest in the outcome of this application, contrary to the allegations of the Examiner.

Thus, the Furness Declaration provides objective evidence that a person of ordinary skill in the art can achieve beneficial results from the SEQ ID NO:1 (NHT) polypeptide in the absence of any knowledge as to the precise function of the protein. The uses of the claimed polypeptides for protein expression monitoring applications including toxicology testing are in fact independent of the function of the polypeptide. Moreover, the claimed invention has numerous other uses as a research tool, each of which alone is a "substantial utility." These include: screening libraries of pharmaceutical agents to identify those which specifically bind NHT in a variety of drug screening techniques; generating antibodies which specifically bind and can identify NHT; and titration of NHT to initially determine the effective dose in cell culture assays or in animal models. (Specification, pages 23-25, 30-31, 36 and 44). Therefore, the uses of the claimed invention in 2-D PAGE gels to assess expression of SEQ ID NO:1 in response to drugs and toxic agents and as a research tool as *disclosed* in the instant specification are well known "real-world" utilities which are credible, specific and substantial utilities attributable to the claimed invention.

C. The Rockett and Iyer Declarations Support the “Well-Established” Utilities of ALL Expressed Proteins, Including NHT, in Protein Expression Profiles Used in Toxicology Studies, Drug Development, and the Phenotypic Characterization and Categorization of Cell types, Including Neoplastic Cell Types and Thus, at Least One Utility for SEQ ID NO:1

In order to demonstrate these points, Appellants direct the Board’s attention to quotes from the Rockett and Iyer Declarations submitted herewith:

"It is widely understood among molecular and cellular biologists that protein expression levels provide complementary profiles for any given cell and cellular state."¹

"Thus, as with nucleic acid microarrays, the greater the number of proteins detectable, the greater the power of the technique; the absence or failure of a protein to change in expression levels does not diminish the usefulness of the method; and prior knowledge of the biological function of the protein is not required. As applied to protein expression profiling, these principles have been well understood since at least as early as the 1980s."²

"It is my opinion, therefore, based on the state of the art in toxicology at least since the mid-1990s -- and as regards protein profiling, even earlier -- that disclosure of the sequence of a new . . . protein, with or without knowledge of its biological function, would have been sufficient information for a toxicologist to use the . . . protein in expression profiling studies in toxicology."³

In his Declaration, Dr. Iyer explains why a person of skill in the art in 1997 would have understood that any expressed polynucleotide is useful for gene expression monitoring applications using cDNA microarrays, stating that “[t]o provide maximum versatility as a research tool, the microarray should include – and as a biologist I would want my microarray to include – each newly identified gene as a probe.” (Iyer Declaration, ¶ 9.)

The Declarations being sufficiently brief, Appellants commend them in their entirety to the Board's attention

¹ Declaration of John C. Rockett, ¶ 11.

² Declaration of John C. Rockett, ¶ 14.

³ Declaration of John C. Rockett, ¶ 18. "Use of the words 'it is my opinion' to preface what someone of ordinary skill in the art would have known does not transform the factual statements contained in the declaration into opinion testimony." *In re Alton*, 37 USPQ2d 1578, 1583 (Fed. Cir. 1996).

II. Appellants' Evidence Demonstrates to One of Ordinary Skill in the Art that NHT is More Likely Than Not a Member of the TUBBY Protein Family

Appellants have established, and one of skill in the art would find Appellants' evidence to demonstrate that, more likely than not, NHT is a member of the TUBBY protein family. The Specification teaches that NHT shares chemical and structural sequence similarity with two TUBBY polypeptides, one from mouse (SEQ ID NO:3) and one from human (SEQ ID NO:4). In particular, NHT shares more than 49% sequence identity with both sequences over its entire length, and is nearly 70% identical with both SEQ ID NO:3 and SEQ ID NO:4, from about amino acid D187 to D436 (numbering on SEQ ID NO:1, about 249 consecutive amino acid residues) (see Specification, page 11, and Figures 2A and 2B).

The Examiner has misconstrued Appellants' and Declarant's reference to NHT as a "novel tubby homolog," citing the "art-accepted meaning of 'homologues.'" (See the Office Action of May 15, 2003, pages 5-6). Although the Examiner's definition of homolog is "art recognized," so too is Appellants' usage. The term homolog, as used in the instant application only, is a comparison of sequences of amino acids or proteins of distantly related species. Thus, the instant application refers to NHT as being a sequence *homolog* to the mouse tub gene (GI 1279766, SEQ ID NO:3) as well as sharing sequence *similarity* to the human tub homolog of the mouse tub gene (GI 1305497, SEQ ID NO:4) (see Specification, page 2, lines 20-22).

Specifically, SEQ ID NO:1 (NHT) is yet another human homolog of the murine tub gene, GI 1279766 (SEQ ID NO:3). However, SEQ ID NO:1 should not be construed to be a homolog of SEQ ID NO:4. Rather, SEQ ID NO:1 and SEQ ID NO:4 share sequence similarity. Additionally, SEQ ID NO:1 shares chemical and structural similarity with the human tub homolog (SEQ ID NO:4) of the murine tub gene (SEQ ID NO:3). Therefore, SEQ ID NO:1 shares chemical and structural homology with SEQ ID NO:3, the mouse tub gene, and is yet another homolog of the mouse tub gene.

A. The similarity of the claimed polypeptide to another of undisputed utility demonstrates utility beyond the reasonable probability required by law

Because the claimed NHT shares homology with the TUBBY gene family, a family in which the members have undisputed utility, evidence of homology can be used to show a substantial likelihood that the claimed polypeptide is similarly useful. Appellants need not show any more to demonstrate utility. Under the applicable law, once the applicant demonstrates a *prima facie* case of homology, the Examiner must accept the assertion of utility to be true unless the Examiner comes forward with evidence showing a person of ordinary skill would doubt the asserted utility could be achieved by a reasonable probability. *See In re Brana*, 51 F.3d at 1566-67; *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974).

As indicated by the final Utility Examination Guidelines (66 FR 1092, January 5, 2001), where the asserted specific, substantial and credible utility for the claimed polypeptide/protein can be based upon homology to existing proteins having an accepted utility, "the asserted utility must be accepted by the examiner unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion." Appellants submit that this Office Action failed to provide sufficient evidence or sound reasoning to rebut Appellants' asserted use of the polypeptide.

In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether the members of the class possess one utility or many. *See Brenner v. Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967); *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973).

In fact, at a recent Biotechnology Customer Partnership Meeting held at the USPTO on April 17, 2001, in a talk by Senior Examiner James Martinell, it was emphasized that Appellants' assertion that his claimed protein "is a member of a family of proteins that [is] already known based upon amino acid sequence homology" can be effective as an assertion of utility for the claimed sequence. According to Dr. Martinell, the proper question for the Examiner to ask, after searching the

prior art for the claimed protein, is "Would one of skill in the art accept that the protein has been placed in the correct family of proteins as is asserted?" The "two" [sic: three] possible answers that can be deduced from this prior art search are, according to Dr. Martinell:

- The search does not reveal any **evidence** that the family attribution made in the application is either **incorrect or may be incorrect**
 - The protein either **more likely belongs to a family other than that asserted** in the application or **likely does not belong to the family asserted** in the application
 - The search shows that the attribution is likely correct
- (From handouts of Dr. Martinell's slides distributed April 17, 2001; emphasis added)

This Office Action has failed to meet the above requirements now recognized by the USPTO. No evidence is cited particular to the claimed protein, e.g., inconsistent findings deduced from the search, upon which to base any objection to the assignment of functional homology to this family of TUBBY proteins. Indeed, there is no such evidence.

In this regard, NHT is *similar* to two TUBBY polypeptides, one from mouse (SEQ ID NO:3) and one from human (SEQ ID NO:4). In particular, NHT shares more than 49% sequence identity over 491 amino acid residues, and is in fact nearly 70% identical with the two sequences from about amino acid D187 to D436 (about 249 amino acid residues) (see specification, page 11, and Figures 2A and 2B).

This is more than enough homology to demonstrate a reasonable probability that the utility of the human TUBBY polypeptides can be imputed to the claimed invention. It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. Brenner et. al., Proc. Natl. Acad. Sci. 95:6073-78 (1998) (Reference No. 5, of record). Given homology in excess of 40% over many more than 70 amino acid residues, the probability that the claimed polypeptide is related to the human TUBBY polypeptides is, accordingly, very high. Additional studies by others of the *TUB* gene family provide further evidence that NHT is a member of the TUBBY protein family.

Appellants submitted in their response of December 13, 2002, the results of a recent BLASTP analysis of SEQ ID NO:1 verses the genpept database (NCBI, version 132). Those results were apparently disregarded by the Office. Had the Office examined the analysis, it would have been

obvious that SEQ ID NO:1 has 99% identity, from residue M1 to residue I439 to tubby-like protein 3 (TULP3, GI21618457), and from 49% to 93% sequence identity to nine additional proteins, all of which are either tubby proteins, TUB homologs, or tubby homologs from either human or mouse (Exhibit A). Clearly, one of ordinary skill in the art would find such evidence to corroborate Appellants' assertion that SEQ ID NO:1 is a member of the TUBBY protein family.

The tubby-like protein 3 has recently been shown to function in signal transduction from heterotrimeric G protein-coupled receptors (Santagata, S. *et al.* (2001) Science 292:2041-2050, Exhibit B, of record). Such a function would more likely than not be applicable to SEQ ID NO:1 as well. Clearly, this is credible, scientific evidence that one skilled in the art would more likely than not conclude that SEQ ID NO:1 is a member of the TUBBY protein family that functions in signal transduction from heterotrimeric G protein-coupled receptors, as seen by the high conservation of residues at the C-terminus.

The Office's citation of Wistow *et al.* is moot, as Appellants' have never asserted that SEQ ID NO:1 and SEQ ID NO:4 have the same biological function (Office Action of May 15, 2003, page 6). Moreover, the teachings of Wistow *et al.* have no relevance to the instant application. Wistow *et al.* address heat-shock proteins and lens crystallins, in contrast, the instant application is directed to a novel TUBBY homolog (Specification, page 2, lines 20-22). SEQ ID NO:1 is yet another homolog of the murine Tubby protein (SEQ ID NO:3) and shares sequence identity with human Tub (SEQ ID NO:4).

Thus, Appellants' have provided corroborating evidence which one of skill in the art would find more likely than not that SEQ ID NO:1 is yet another homolog to the mouse TUBBY polypeptide and a member of the TUBBY protein family. Therefore, Appellants have met the standard of proof and the Office's evidence to the contrary refuting Appellants' findings is not applicable.

It is undisputed that the claimed polypeptide is a protein having the sequence shown as SEQ ID NO:1 in the patent application and referred to as NHT in the application. Moreover, since there is a substantial likelihood that the claimed polypeptide is a member of the TUBBY gene family, and the members are indisputably useful, there is by implication a substantial likelihood that the claimed polypeptide is similarly useful. Appellants need not show any more to demonstrate utility. Therefore, the Examiner must accept Appellants' demonstration that the claimed polypeptide is a member of the

TUBBY proteins and that the utility is proven by a reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. *See In re Langer*, 503 F.2d 1380, 1391-1392, 183 USPQ 288 (CCPA 1974).

The final Utility Examination Guidelines further provides that

[w]hen a class of proteins is defined such that the members share a specific, substantial, and credible utility, the reasonable assignment of a new protein to the class of sufficiently conserved proteins would impute the same specific, substantial, and credible utility to the assigned protein.

This Office Action offers no evidence that the members of this class of TUBBY proteins do not share a specific, substantial functional attribute or utility, despite having structural features in common. Thus, this strongly indicates that any member of this TUBBY protein class would have some patentable utility. It follows that there is a more substantial likelihood that the claimed polypeptide also has a patentable utility, regardless of its actual function. The law has never required a patentee to prove more.

It appears from the statements of the Office Action that Appellants are being required to assert a rigorous correlation to establish the identity of NHT as a member of the TUBBY family as well as to establish a specific disease affected by NHT. However, the final Utility Examination Guidelines provides that

[A] “rigorous correlation” need not be shown in order to establish practical utility; “reasonable correlation” is sufficient. *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1565, 39 USPQ2d 1895, 1900 (Fed Cir. 1996).

The Examiner must accept the Appellants’ demonstration that the homology between the claimed invention and TUBBY polypeptides demonstrates utility by a reasonable probability, and additionally, that the claimed polypeptide is a member of the TUBBY gene family unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. *See In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Examiner has not provided sufficient evidence or sound scientific reasoning to the contrary.

1. SEQ ID NO:1 has the Utility of TULP3

The Office has refused to accept that 99% sequence identity between SEQ ID NO:1 and TULP3 provides a utility for SEQ ID NO:1, i.e., functioning in signal transduction from heterotrimeric G protein coupled receptors (Office Action of May 15, 2003, page 8). The Examiner offers no basis to support the Examiner's disbelief of Appellants' asserted function. Given this lack of explicit support, Appellants can only assume that the Examiner is relying on facts within her personal knowledge that lead her to disregard the proffered evidence. She is in effect holding herself out as one of ordinary skill in the art. Thus, Appellants request an affidavit from the Examiner in support of this basis for rejection, in keeping with 37 C.F.R. §104(d)(2).

2. Constructive Reduction to Practice Constitutes Conception of Utility

Appellants' constructive reduction to practice of the instant application constitutes good and sufficient conception of the utility of SEQ ID NO:1 as disclosed in the instant application. However, the Office asserts that the Santagata et al., 2001 paper is a "post-filing date, and cannot be relied upon to establish what was known about TULP proteins at the time the invention was made" (Office Action of May 15, 2003, page 9).

The instant application is replete with disclosures of functions for SEQ ID NO:1. Appellants' assertion that TUBBY proteins are involved in appetite and eating disorders is based on the function of the murine Tubby homolog (SEQ ID NO:3). So too, SEQ ID NO:1, again based on its homology to murine tubby (SEQ ID NO:3), finds additional uses by virtue of the association of Tubby with progressive retinal degeneration and hearing loss, as well as maturity onset diabetes and insulin resistance. Further, sensory defects may be associated with cGMP induced, phosphodiesterase mediated apoptotic activity (See Specification, page 2, lines 9-13). Thus, SEQ ID NO:1 also finds use in the study of ocular diseases.

B. The Office has Failed to Consider All of the Evidence Presented by Appellants to Establish Utility for the Claimed Invention

The Examiner has asserted that Appellants cannot rely upon the Santagata et al. 2001 publication, because it is a "post-filing date, and cannot be relied upon to establish what was known

about TULP proteins at the time the invention was made” (Office Action of May 15, 2003, page 9). It is Appellants’ position that the Santagata et al. paper is further *supporting evidence* that SEQ ID NO:1 is a member of the Tubby gene family. Such evidence is required to be given “due consideration.”

Section 2701.02 of Manual of Patent Examining Procedure (original 8th edition, published August, 2001, latest revision February 2003) (hereinafter “MPEP”) provides:

If a rejection under 35 U.S.C. 101 has been properly imposed, along with a corresponding rejection under 35 U.S.C. 112, first paragraph, the burden shifts to the applicant to rebut the prima facie showing. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992) (“The examiner bears the initial burden, on review of the prior art or on any other ground, of presenting a prima facie case of unpatentability. . . . After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, *by a preponderance of evidence with due consideration to persuasiveness of argument.*”). *An applicant can do this using any combination of the following: amendments to the claims, arguments or reasoning, or new evidence submitted in an affidavit or declaration under 37 CFR 1.132, or in a printed publication.* . . . (emphasis added)

If the applicant responds to the prima facie rejection, Office personnel should review the original disclosure, any evidence relied upon in establishing the prima facie showing, any claim amendments, and any new reasoning or evidence provided by the applicant in support of an asserted specific and substantial credible utility. It is essential for Office personnel to recognize, fully consider and respond to each substantive element of any response to a rejection based on lack of utility. Only where the totality of the record continues to show that the asserted utility is not specific, substantial, and credible should a rejection based on lack of utility be maintained. *If the record as a whole would make it more likely than not that the asserted utility for the claimed invention would be considered credible by a person of ordinary skill in the art, the Office cannot maintain the rejection. In re Rinehart, 531 F.2d 1048, 1052, 189 USPQ 143, 147 (CCPA 1976).* (emphasis added)

Id at page 2100-42-43.

Appellants’ reiterate in their entirety arguments and reasoning presented to the Office in their response filed December 13, 2002 pertaining not only to the membership of SEQ ID NO:1 in the tubby gene family, but also evidence of the function of TULP3 and therefore, more likely than not, an asserted

function and utility for SEQ ID NO:1. Appellants respectfully ask the Office to abide by the practices set forth in the MPEP and established by case law.

C. Membership in a Class of Useful Products Can Be Proof of Utility

Despite evidence that the claimed polypeptide is a member of the TUBBY gene family, whose members indisputably are useful, the Examiner refused to impute the utility of the members of the TUBBY gene family to NHT. In the Office Action of September 24, 2002, the Patent Examiner takes the position that, "[t]he assertion that the disclosed NHT has biological activities similar to known TUBBY cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities." (Office Action of September 24, 2002, page 3, ¶ 3). To demonstrate utility by membership in the class of TUBBY polypeptides, the Examiner would require that all TUBBY polypeptides possess a "common" utility.

The Examiner has not provided any evidence that any member of the TUBBY gene family, let alone a substantial number of those members, is not useful. In such circumstances the only reasonable inference is that the claimed polypeptide must be, like the other members of the TUBBY gene family, useful.

Even if the Examiner's "common utility" criterion were correct, the TUBBY gene family would meet it. It is undisputed that known members of the TUBBY gene family function in signal transduction from heterotrimeric G protein-coupled receptors. A person of ordinary skill in the art need not know any more about how the claimed invention functions in signal transduction from heterotrimeric G protein-coupled receptors to use it, and the Examiner presents no evidence to the contrary. Instead, the Examiner makes the conclusory observation that a person of ordinary skill in the art would need to know whether, for example, any given TUBBY polypeptide functions in signal transduction from heterotrimeric G protein-coupled receptors. The Examiner then goes on to assume that the only use for NHT absent knowledge as to how this member of the TUBBY gene family actually works is further study of NHT itself. However, this assumption is incorrect.

As disclosed by Appellants, knowledge that NHT is a TUBBY-like polypeptide is more than sufficient to make it useful for the diagnosis and treatment of appetite and eating disorders and ocular diseases. Indeed, NHT has been shown to be expressed in brain, neuronal and lymph node cDNA libraries. The Examiner must accept these facts to be true unless the Examiner can provide evidence or sound scientific reasoning to the contrary. But the Examiner has not done so.

D. The Patent Examiner Failed to Demonstrate That a Person of Ordinary Skill in the Art Would Reasonably Doubt the Utility of the Claimed Invention

Appellants have shown that NHT shares homology with the TUBBY gene family, a family consisting of members known to have undisputed utility, and therefore, homology can be used to show a substantial likelihood that the claimed polypeptide is similarly useful. Appellants need not show any more to demonstrate utility. Specifically, the TUBBY family includes TULP3 which shares 99% sequence identity with NHT. TULP3 has been demonstrated to function in signal transduction from heterotrimeric G protein-coupled receptors. Based on the high level of sequence homology, structural characteristics and tissue expression, Appellants have demonstrated a *prima facie* case for homology as an acceptable assertion of utility of the claimed polypeptides. Such an assertion of utility would be determined to be sound scientific reasoning by one skilled in the art. Therefore, the Examiner must accept the Appellants' demonstration by homology that the claimed polypeptide is a member of the TUBBY gene family and that the homology between the claimed invention and TUBBY polypeptides demonstrates utility by a reasonable probability, unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility.

Under the applicable law, once the applicant demonstrates a *prima facie* case of homology, the Examiner must accept the assertion of utility to be true unless the Examiner comes forward with evidence showing a person of ordinary skill would doubt the asserted utility could be achieved by a reasonable probability. See *In re Brana*, 51 F.3d at 1566; *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974).

Moreover, as indicated by the final Utility Examination Guidelines (66 FR 1092, January 5, 2001), where the asserted specific, substantial and credible utility for the claimed polypeptide/protein

can be based upon homology to existing proteins having an accepted utility, "the asserted utility must be accepted by the examiner unless the Office has sufficient evidence or sound scientific reasoning to rebut such an assertion." Appellants submit that this Office Action failed to provide sufficient evidence or sound reasoning to rebut Appellants' asserted use of the polypeptide.

The literature cited by the Examiner *infra* is not inconsistent with the Appellants' proof of homology by a reasonable probability. It may show that Appellants cannot prove function by homology with **certainty**, but Appellants need not meet such a rigorous standard of proof. The literature cited identifies some of the difficulties involved in predicting biological activity, or membership in a protein family, though none suggest that functional homology cannot be inferred by a reasonable probability as in this case. The Examiner rejected the pending claims on the ground that the applicant cannot "credibly" impute utility to the claimed invention based on its 49% homology to another polypeptide undisputed by the Examiner to be useful. The Examiner's rejection is both incorrect as a matter of fact and as a matter of procedural law.

In the present case, the Office Action alleges that the amino acid sequence identity between NHT and known TUBBY proteins is insufficient to establish that NHT is a member of the TUBBY family of proteins because "[t]he assertion that the disclosed NHT has biological activities similar to known TUBBY cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities" (Office Action, filed September 24, 2002, page 3). The Examiner cites Tischer *et al.* (U.S. Patent 5,194,596), Benjamin *et al.* (1998), Vukicevic *et al.* (1996), North *et al.* (1997), Gu *et al.* (1998) and Hayes *et al.* (1998) as support to doubt Appellants asserted utility. Importantly, all of these documents fail to **specifically** support the outstanding rejections because none of them are specifically relevant to the TUBBY protein family. Moreover, none of them contradict Brenner's basic rule that sequence homology in excess of 40% over 70 or more amino acid residues yields a high probability of functional homology as well. At most, these articles individually and together stand for the **general** proposition that it is difficult to make predictions about function or biological activity with certainty.

The Examiner further cited Haynes *et al.* in support of the Examiner's assertion that nucleic acid levels are not predictive of protein levels. The Northern data presented by Appellants represents evaluation of human tissue expression patterns. The Haynes *et al.* conclusion is based on the yeast *Saccharomyces cerevisiae* growing at mid-log phase, and is therefore of very limited relevance. Only 80 *S. cerevisiae* (vs. human) proteins were selected for evaluation. No where is it taught that NHT was one of the proteins evaluated. Therefore, the Haynes *et al.* paper does not teach the expression levels of SEQ ID NO:1 and does not teach away from Appellants' position that SEQ ID NO:1 was expressed in brain and neuronal tissues and in lymph node tissues. Additionally, the findings of Santagata *et al.* support Appellants' assertions that expression of SEQ ID NO:1 is predominately located in the brain.

Thus, the Haynes *et al.* paper is utterly irrelevant to the instant invention. The Examiner has attempted to broadly apply a citation which does not teach Appellants' invention. This citation does not constitute either evidence or sound scientific reasoning to show that a person of ordinary skill in the art would reasonably doubt Appellants' invention lacked patentable utility.

The Office's attention is further directed to Brenner *et al.*, *supra* that teaches through exhaustive analysis of a data set of proteins with **known** structural and functional relationships and with <90% overall sequence identity, that 30% identity has been determined to be a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues. (Brenner *et al.*, pages 6073 and 6076.) As shown in the Figures and as discussed in the specification, SEQ ID NO:1 shares 49% identity with at least two known TUBBY proteins over at least 491 residues, and nearly 70% identity over 249 residues, vastly exceeding this threshold. Moreover, recent BLASTP analysis actually confirms that NHT is a possible splice variant of TULP-3, by demonstrating that 99% sequence identity exists between the two proteins. Since these criteria are based on a data set of known homologous proteins with shared structural and functional features, one of ordinary skill in the art would reasonably expect the polypeptides of the invention possess the evolutionarily conserved **structural and functional** characteristics of a TUBBY protein.

It is known in the art that natural selection acts to conserve protein function. Conversely, mutations that reduce or abolish protein function are usually eliminated by natural selection. Based on

these central tenets of molecular evolution, Appellants put forth that the amino acid differences among Appellants' polypeptide and the known TUBBY proteins, are likely to occur at positions of minimal functional importance, while residues that are conserved are likely those that are important for protein function. One of ordinary skill in the art would therefore conclude that, more likely than not, the level of conservation observed between Appellants' polypeptide and the two known human TUBBY proteins are indicative of a common function, and hence common utility, among these proteins.

In conclusion, the preponderance of evidence therefore does not support the Examiner's basis for the rejection of claims under 35 U.S.C. § 101. The only relevant evidence of record shows that a person of ordinary skill in the art would not doubt that the claimed polypeptide is in fact a member of the TUBBY family of proteins, which are known to have specific utility.

IV. The diagnosis and treatment of maturity onset diabetes, insulin resistance, progressive retinal degeneration and hearing loss as well as appetite and eating disorders are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. Additionally, these uses are explained, in detail, in the Furness Declaration, discussed *supra*. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

The specification teaches that NHT is a member of the TUBBY polypeptide family and that defects in *TUB* genes and in TUBBY expression have been found in maturity onset diabetes, insulin resistance, progressive retinal degeneration and hearing loss (see specification, page 2, lines 9-10). Appellants have presented evidence that the claimed invention would have the utilities of TUBBY proteins, proteins which are known to be involved in appetite and eating disorders. Therefore, one of ordinary skill in the art would conclude that, more likely than not, that NHT would also have these uses. Thus, the claimed invention meets the utility requirements under 35 U.S.C. §§ 101 and 112, first paragraph.

V. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Examiner Misstate the Law

There is an additional, independent reason to withdraw the rejections. To the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: “specific” utilities, which meet the statutory requirements, and “general” utilities, which do not. The Training Materials define a “specific utility” as follows:

A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as “gene probe” or “chromosome marker” would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between “specific” and “general” utilities by assessing whether the asserted utility is sufficiently “particular,” *i.e.*, unique (Training Materials at p.52) as compared to the “broad class of invention.” (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82 J.P.T.O.S. 77, 97 (Feb. 2000) (“With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.”).)

Such “unique” or “particular” utilities never have been required by the law. To meet the utility requirement, the invention need only be “practically useful,” *Natta*, 480 F.2d 1 at 1397, and confer a “specific benefit” on the public. *Brenner*, 383 U.S. at 534. Thus incredible “throwaway” utilities, such as trying to “patent a transgenic mouse by saying it makes great snake food,” do not meet this standard.

Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where “specific utility” is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be “definite,” not particular. *Montedison*, 664 F.2d at 375. Appellants are not aware of any court that has rejected an assertion of utility on the grounds that it is not “particular” or “unique” to the specific invention. Where courts have found utility to be too “general,” it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had “useful biological activity” was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. See *Brana, supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a “particular” type of cancer was determined to satisfy the specificity requirement). “Particularity” is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § III.B. (*Montedison*, 664 F.2d at 374-75).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of “general” utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions heretofore considered to be patentable, and that have indisputably benefitted the public, including the claimed invention. See *supra* § III.B. Thus, the Training Materials cannot be applied consistently with the law.

ISSUE 2: The Rejection of Claim 1, 2, 16 and 17 under 35 U.S.C. § 112, first paragraph is Improper to the Extent it is Based on the Improper Allegation of Lack of Patentable Utility

- A. **To the extent the rejection of the claimed invention under 35 U.S.C. § 112, first paragraph, is based on the improper rejection for lack of utility under 35 U.S.C. § 101, it must be reversed.**

The rejection set forth in the Office Actions of *September 9, 2002 and May 15, 2003* is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under § 112, first paragraph, is based on the improper allegation of lack of patentable utility under § 101, it fails for the same reasons.

Appellants respectfully submit that rejections for lack of utility, based *inter alia*, on an allegation of “lack of specificity,” as set forth in the Office Actions and as justified in the Revised Interim and final Utility Guidelines and Training Materials, are not supported in the law. Neither are they scientifically correct, nor supported by any evidence or sound scientific reasoning. These rejections are alleged to be founded on facts, yet those facts are clearly distinguishable from the facts of the instant application, and indeed most if not all nucleotide and protein sequence applications. Nevertheless, the PTO is attempting to mold the facts and holdings of these prior cases, “like a nose of wax,”⁴ to target rejections of claims to polypeptide and polynucleotide sequences, as well as to claims to methods of detecting said polynucleotide sequences, where biological activity information has not been proven by laboratory experimentation, and they have done so by ignoring perfectly acceptable utilities fully disclosed in the specifications as well as well-established utilities known to those of skill in the art. As is disclosed in the specification, and even more clearly, as one of ordinary skill in the art would understand, the claimed invention has well-established, specific, substantial and credible utilities. The rejections are, therefore, improper and should be reversed.

⁴“The concept of patentable subject matter under §101 is not ‘like a nose of wax which may be turned and twisted in any direction * * *.’ *White v. Dunbar*, 119 U.S. 47, 51.” (*Parker v. Flook*, 198 USPQ 193 (US SupCt 1978))

Moreover, to the extent the above rejections were based on the Revised Interim and final Examination Guidelines and Training Materials, those portions of the Guidelines and Training Materials that form the basis for the rejections should be determined to be inconsistent with the law.

ISSUE 3: The Rejection under 35 U.S.C. §112, first paragraph Is Improper, as the Specification Provides an Adequate Written Description as Claimed

Claims 1 and 16 stand rejected under the first paragraph of 35 U.S.C. §112 for allegedly containing subject matter “not described in the specification in such a way as too reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons cited in the previous Office Action paper number 7, at pages(s) 6-7.”

The Office Action asserts that:

- . . . the specification provides SEQ ID NO: 1. No naturally occurring variants thereof are described, . . . (Office Action of September 9, 2002, page 6).
- . . . No other naturally occurring sequences have been described as obtainable from human, nor any other animal. A breadth of 90% would reasonably be expected to encompass homologues obtained from other primate species such as macaque, rhesus, gibbon, as well as from non-primate species, such as rat or mouse, giraffe, hippo or even frog or yeast, depending upon the evolutionary conservation of the protein in question (Office Action of May 15, 2003, p. 11)
- . . . There is no description of the function of the protein, such as would allow one of skill in the art to predict what portions of the disclosed sequence would be expected to be conserved. With further respect to this issue, it is a protein that is being claimed; without having a written description of all naturally occurring sequences within the metes and bounds of the claims, one would not be capable of determining whether or not a given species was claimed (Office Action of May 15, 2003, pages. 11-12)
- At page 34, appellants argue that one of ordinary skill in the art would recognize naturally occurring variants of SEQ ID NO: 1 having 90% identity to SEQ ID NO: 1; this is not true. One could certainly determine whether a protein that one had obtained from nature were 90% identical to SEQ ID NO: 1, but that same person, handed a protein in a test tube, would have no way of

determining whether that protein were 'naturally occurring' (Office Action of May 15, 2003, page 12)

This rejection is respectfully traversed.

Appellants reiterate their arguments filed December 13, 2002 and are incorporated herein as if reiterated in full.

Clearly, it appears that the Examiner has apparently confused this instant application and the responses filed by Appellants with those by another. Appellants respectfully request that the Examiner fully review the response filed December 13, 2002, especially pages 33-36 as well as the Office Action Summary (Paper #7) which indicate that the Office Action of September 24, 2002 was a non-final action and thus the comments were incorrectly addressed to "Appellant(s)". A written statement of this fact, for the record is respectfully requested.

A. The Applicable Legal Standard

The requirements necessary to fulfill the written description requirement of 35 U.S.C. § 112, first paragraph, are well established by case law.

. . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the "written description" inquiry, *whatever is now claimed*. *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

. . . Mention of representative compounds encompassed by generic claim language *clearly is not required by Section 112 or any other provision of the statute*. But, where no explicit description of a generic invention is to be found in the specification...mention of representative compounds may provide an implicit description upon which to base generic claim language. *In re Robins*, 429 F.2d 452, 456-57, 166 USPQ 552, 555 (CCPA 1970) [emphasis added]

. . . [I]t has been consistently held that the naming of one member of such a group is not, in itself, a proper basis for a claim to the entire group. However, *it may not be necessary to enumerate a plurality of species if a genus is sufficiently*

identified in an application by 'other appropriate language.' *In re Grimme*, 274 F.2d 949, 952, 124 USPQ 499, 501 (CCPA 1960) [emphasis added]

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that:

An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., ***complete or partial structure***, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. ***If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.*** [emphasis added] [footnotes omitted]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

1. The specification provides an adequate written description of the claimed "variants" of SEQ ID NO:1

The subject matter encompassed by Claims 1 and 16 are either disclosed by the specification or conventional or well known to one skilled in the art.

Independent claim 1 recites "An isolated polypeptide selected from the group consisting of: a) a polypeptide comprising an amino acid sequence of SEQ ID NO:1, and b) a polypeptide comprising a naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, said polypeptide retaining at least one function of a polypeptide comprising an amino acid sequence of SEQ ID NO:1." The Examiner's position is based upon the theory that the Specification provides an adequate written description of SEQ ID NO:1 and that "One could certainly determine whether a protein that one had obtained from nature were 90% identical to SEQ ID NO: 1 (Office Action of May 15, 2003). However, the Specification allegedly lacks an adequate written description

of the variant polypeptides because, “No naturally occurring variants thereof are described” (Office Action of September 24, 2002 at page 6). Appellants strongly disagree with this position.

Such a position ignores that the polypeptides recited in claim 1) *are* described in terms of their structure. That is, the claimed polypeptides are “*at least 90% identical to the amino acid sequence of SEQ ID NO:1.*” The structure of SEQ ID NO:1 is provided in the specification, for example, at pages 46-47 of the Sequence Listing and Figures 1A, 1B, 1C and 1D for SEQ ID NO:1. The phrases “percent identity” or “% identity” as well as methods for determining such identity are well known to the skilled artisan. Claim 1, as previously amended, does not encompass any peptide or protein with altered sequence, but rather is limited to those having at least 90% amino acid sequence identity to SEQ ID NO:1.

Appellants submit that this description is sufficient to describe the claimed genus based on the disclosure of the single species, SEQ ID NO:1, for reasons stated in the USPTO’s own training materials for implementation of the Written Description Guidelines under 35 USC § 112, first paragraph. In the “Synopsis of Application of Written Description Guidelines” (USPTO Website www.uspto.gov, March 1, 2000), at page 53 of these guidelines, a claim to “A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A → B” is considered to meet the written description requirements because:

--- procedures for making variants of SEQ ID NO:3 are conventional in the art and an assay is described which will identify all other proteins having the claimed catalytic activity. Moreover, procedures for making variants of SEQ ID NO:3 which have 95% identity to SEQ ID NO:3 and retain its activity are conventional in the art.

The Guidelines further state:

The single species disclosed (SEQ ID NO:3) is representative of the genus because all member have at least 95% structural identity with the reference compound and because of the presence of an assay which applicant provided for identifying all of the at least 95% identical variants of SEQ ID NO:3 which are capable of the specified catalytic activity.

A detailed description of the chemical and structural features of SEQ ID NO:1 which contribute to the characterization of SEQ ID NO:1 and other related proteins related to the TUBBY gene family are provided, for example, at p. 11, lines 1-10 and Figures 2A, 2B, 3A and 3B. Ninety percent variants of the claimed polypeptides are described, for example, at p. 11, lines 13-15.

When provided with the detailed description as noted above, one of ordinary skill in the art “would have understood the inventor to be in possession of the claimed invention at the time of filing.” That is, one of ordinary skill in the art would recognize polypeptide sequences which are variants at least 90% identical to SEQ ID NO:1. Given a polypeptide sequence, it would be routine for one of skill in the art to recognize whether it was a variant of SEQ ID NO:1 and to determine the % identity to SEQ ID NO:1 of the variant. Accordingly, the specification provides an adequate written description of the recited variants of SEQ ID NO:1.

2. The specification provides an adequate written description as required by law

Appellants submit that case law in the area of the written description requirement of 35 U.S.C. 112, first paragraph is clear with regard to the details considered sufficient to describe a claimed genus:

. . . Mention of representative compounds encompassed by generic claim language *clearly is not required by Section 112 or any other provision of the statute*. But, where no explicit description of a generic invention is to be found in the specification . . . mention of representative compounds may provide an implicit description upon which to base generic claim language. *In re Robins*, 429 F.2d 452, 456-57, 166 USPQ 552, 555 (CCPA 1970) [emphasis added]

. . . [I]t has been consistently held that the naming of one member of such a group is not, in itself, a proper basis for a claim to the entire group. However, *it may not be necessary to enumerate a plurality of species if a genus is sufficiently identified in an application by ‘other appropriate language.’* *In re Grimme*, 274 F.2d 949, 952, 124 USPQ 499, 501 (CCPA 1960) [emphasis added]

The specification sets forth a description of the claimed polypeptide variants using “other appropriate language” as indicated above in connection with the remarks regarding an amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1”. The claimed variants have been described in terms of their relationship to the chemical structure of SEQ ID NO:1 and structural requirements at, for example, pp. 46-47 of the Sequence Listing; Figures 1A, 1B, 1C, and 1D; p. 11, lines 1-10 and Figures 2A, 2B, 3A and 3B. The specification provides a means of identifying functional variants having 90% sequence identity with SEQ ID NO:1 at, for example, p. 11, lines 1-10. Appellants therefore submit that the “genus is sufficiently identified in [the instant]

application by ‘other appropriate language’” as stated in *In re Grimme*, 274 F.2d 949, 952, 124 USPQ 499, 501 (CCPA 1960). Furthermore, Appellants submit that “a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing” as stated in the Patent and Trademark Office’s own “Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1”, published January 5, 2001. Accordingly, Claim 2 meets the statutory requirements for written description under 35 U.S.C. 112, first paragraph.

3. Conclusion

The Final Office Action failed to base its written description inquiry pertinent to the present claims in view of their scope. In particular, the subject matter of the claims of the instant application is defined in terms of the chemical structure of SEQ ID NO:1. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polypeptides defined by the present claims is adequately described, as evidenced by specific passages of the specification as set forth above. Furthermore, the Examiner has applied to the subject application a written description standard that has no basis in the law.

For at least the above reasons it is believed that Claims 1 and 16 meet the written description requirement of 35 U.S.C. § 112, first paragraph. It is therefore requested that this rejection be reversed.

ISSUE 4: The Rejection under 35 U.S.C. §112, second paragraph, for Indefiniteness is Improper, as the Specification Clearly and Distinctly Claims the Subject Matter of the “Invention” and Determines the Metes and Bounds of Claim 1

Claims 1, 2, 16 and 17 were rejected as indefinite for allegedly “failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention” and further that, “[a]s no naturally occurring sequences having 90% identity to Seq ID NO: 1 are described, the metes and bounds of claim 1 cannot be determined. It cannot be determined which 90% identical sequences are or are not naturally occurring” (Office Action of May 15, 2003, pages 12-13). The Examiner stated that “[t]he sequence and structural properties in no way reveal the origin of the molecule or its

forebears,” and [c]laims 2, 16 and 17 are rejected for depending from an indefinite claim.” (Office Action of May 15, 2003, page 13).

The standard for “definiteness” is that the claims define patentable subject matter with a reasonable degree of precision and particularity. See *In re Miller*, 169 USPQ 597, 599 (CCPA 1971); *In re Moore*, 169 USPQ 236, 238 (CCPA 1971). See also MPEP §706.03(d). In this regard, the Supreme Court has indicated that the primary purpose of claim language is to give “fair” notice of what would constitute the infringement of a claim. See *United Carbon Co. v. Binny & Smith Co.*, 317 U.S. 228, 55 USPQ 381 (1942). In other words, the basic purpose of 35 U.S.C. §112, second paragraph is to require a claim to reasonably apprise those skilled in the art of the scope of the invention defined by that claim and give fair notice of what constitutes infringement of the claim. See *Antonious v. Pro Group Inc.*, 217 USPQ 875, 877 (6th Cir. 1983).

At pages 4-5 of the specification, Appellants define “naturally occurring” as “substantially purified NHT obtained from any species, particularly mammalian, including bovine, ovine, porcine, murine, equine, and preferably human, from any source whether natural, synthetic, semi-synthetic, or recombinant” (specification, page 4 line29 to page 5 line 1). Thus, the term “naturally occurring” would be understood by one of skill in the art and even by an unskilled person of the art to be that which occurs in nature. Further, “variants” are defined at page 5, lines 9-17, as referring to “an amino acid sequence that is altered by one or more amino acids.”

Given that Appellants define “portion” as “with regard to a protein (as in “a portion of a given protein”) refers to fragments of that protein” (specification, page 8 lines 21-25), and “alteration” as, “in the polynucleotide of SEQ ID NO:2, as used herein, comprise any alteration in the sequence of polynucleotides encoding NHT including deletions, insertions, and point mutations . . .” (specification, page 9 line 30 to page 10 line 9), and the fact that Appellants separately claim variants of SEQ ID NO:1, in subsection a) and b) of claim 1, one of ordinary skill would easily understand the term “variants” to include those naturally occurring molecules which exhibit the specified degree of sequence identity over the entire length of SEQ ID NO:1.

Hence the meaning is clear, and Appellants therefore respectfully request reversal of the rejection.

ISSUE 5: The Rejection of Claims 1 and 16 under 35 U.S.C. §102 (e) is Improper, as the Cited Reference Fails to Disclose All Elements and Limitations of the Rejected Claims

Appellants traverse the rejection of claims 1 and 16 for at least the following reasons. Kleyn *et al.* do not teach either a polypeptide comprising SEQ ID NO:1 or polypeptides having 90% sequence identity to SEQ ID NO:1; therefore, claims 1 and 16 are not anticipated by Kleyn *et al.* Additionally, although not acquiescing to the stated reason for the rejections of claims 1 and 16, claim 1 c) has been deleted. The amendment removes recitation of “a biologically-active fragment of a polypeptide having the amino acid sequence of SEQ ID NO:1, said polypeptide retaining at least one function of a polypeptide comprising an amino acid sequence of SEQ ID NO:1.” Therefore, claims 1 and 16 are not anticipated by Kleyn *et al.* and reversal of this rejection is requested.

(9) CONCLUSION

Appellants respectfully submit that rejections for lack of utility based, *inter alia*, on an allegation of "lack of specificity," as set forth in the Office Actions and as justified in the Revised Interim and final Utility Guidelines and Training Materials, are not supported in the law. Neither are they scientifically correct, nor supported by any evidence or sound scientific reasoning. These rejections are alleged to be founded on facts in court cases such as *Brenner* and *Kirk*, yet those facts are clearly distinguishable from the facts of the instant application, and indeed most if not all nucleotide and protein sequence applications. Nevertheless, the PTO is attempting to mold the facts and holdings of these prior cases, "like a nose of wax,"⁵ to target rejections of claims to polypeptide and polynucleotide sequences, as well as to claims to methods of detecting said polynucleotide sequences, where biological activity information has not been proven by laboratory experimentation, and they have done so by ignoring perfectly acceptable utilities fully disclosed in the specifications as well as well-established utilities known to those of skill in the art. As is disclosed in the specification, and even more clearly, as one of ordinary skill in the art would understand, the claimed invention has well-established, specific, substantial and credible utilities. The rejections are, therefore, improper and should be reversed.

Moreover, to the extent the above rejections were based on the Revised Interim and final Examination Guidelines and Training Materials, those portions of the Guidelines and Training Materials that form the basis for the rejections should be determined to be inconsistent with the law.

Additionally, the inexplicable lack of consideration by the Office of Appellants' arguments and evidence presented in the response filed September 15, 2003, results in an Office Action rife with misstatements and errors as well as an incomplete examination. Thus, Appellants must waste valuable time and resources to maintain the pendency of the instant application while the Office corrects its failure to dutifully examine and establish a complete record of examination. Thus, Appellants submit that had the Office fully considered the arguments and evidence presented to the Office in the response

⁵"The concept of patentable subject matter under §101 is not 'like a nose of wax which may be turned and twisted in any direction * * *.' *White v. Dunbar*, 119 U.S. 47, 51." (*Parker v. Flook*, 198 USPQ 193 (US SupCt 1978))

filed September 15, 2003, that the instantly claimed invention would have been found too met the requirements of utility, written description, definiteness and is not anticipated as evidenced by the reasons, arguments and Declarations submitted in the response filed September 15, 2003. Therefore, Appellants respectfully request that all of the outstanding grounds of rejection, as addressed in this Brief on Appeal, be reversed.

Due to the urgency of this matter and its economic and public health implications, an expedited review of this appeal is earnestly solicited.

If the USPTO determines that any additional fees are due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108**.

This brief is enclosed in triplicate.

Respectfully submitted,

INCYTE CORPORATION

Date: 24, November 2003

Shirley A. Recipon
Shirley A. Recipon
Reg. No. 47,016
Direct Dial Telephone: (650) 621-8555

Date: 11/24/03

Cathleen M. Rocco
Cathleen M. Rocco
Reg. No. 46,172
Direct Dial Telephone: (650) 845-4587

Customer No.: 27904
3160 Porter Drive
Palo Alto, California 94304
Phone: (650) 855-0555
Fax: (650) 849-8886

Enclosures:

1. Declaration of Declaration of John C. Rockett, Ph.D., under 37 C.F.R. §1.132, with Exhibits A - Q
2. Declaration of Vishwanath R. Iyer, Ph.D., under 37 C.F.R. § 1.132 with Exhibits A - E

APPENDIX - CLAIMS ON APPEAL

Claim 1 An isolated polypeptide selected from the group consisting of:

- a) a polypeptide comprising an amino acid sequence of SEQ ID NO:1, and
- b) a polypeptide comprising a naturally-occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1, said polypeptide retaining at least one function of a polypeptide comprising an amino acid sequence of SEQ ID NO:1.

Claim 2 An isolated polypeptide of claim 1, comprising the amino acid sequence of SEQ ID NO:1.

Claim 16 A composition comprising a polypeptide of claim 1.

Claim 17 A composition of claim 16, wherein the polypeptide comprises the amino acid sequence of SEQ ID NO:1.